AUG 8 1925 Medical Lib

VOL. CLXX, No. 2 AUGUST, 1925 No. 641

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

E. B. KRUMBHAAR, M.D., EDITOR
RICHARD A. KERN, M.D., ASSISTANT EDITOR

ESTABLISHED 1820

A CONSIDERATION OF THE CLINICAL VALUE OF EPHEDRIN, WITH A REPORT ON ITS EFFECTS IN CERTAIN SPECIAL CASES. By T. GRIER MILLER, M.D. 157

ONE HUNDRED CONSECUTIVE CHOLECYSTECTOMIES. By WILLIAM O. JOHNSON, M.D. . 181

A REVIEW OF TWENTY-EIGHT CASES OF PURPURA HEMORRHAGICA IN WHICH SPLENECTOMY WAS PERFORMED. By HERBERT Z. GIFFIN, M.D., and JACKSON K. HOLLOWAY, M.D. 186

A CLINICAL STUDY OF QUINIDIN THERAPY. By HERMAN H. RIECKER, M.D. 205

EXPERIMENTAL GASTRIC AND DUODENAL INFLAMMATION AND ULCER. By ALBERT HOFFMANN 212

THE SIGMOIDOSCOPIC PICTURE OF CHRONIC ULCERATIVE COLITIS (NON-SPECIFIC). By BURRILL B. CROHN, M.D., and HERMAN ROSENBERG, M.D. 220

THE POSSIBLE RELATIONSHIP BETWEEN GUANIDIN AND HIGH BLOOD PRESSURE. By RALPH H. MAJOR, M.D. 228

CALORIMETRIC STUDIES OF THE EXTREMITIES FOLLOWING LUMBAR SYMPATHETIC RAMISECTION AND GANGLIONECTOMY. By GEORGE E. BROWN, M.D., and ALFRED W. ADSON, M.D. 232

DISEASE OF THE CORONARY ARTERIES. By M. H. NATHANSON 240

RECTAL ETHER ANALGESIA IN CHILDBIRTH. By JAMES A. HARRAR, M.D. 256

A REPORT OF AN INTERESTING TYPE OF DIAPHRAGMATIC HERNIA OF THE CARDIA OF THE STOMACH THROUGH THE ESOPHAGEAL ORIFICE. By JULIUS FRIEDENWALD, M.D., and MAURICE FELDMAN, M.D. 263

IODIN HYPERTHYROIDISM. By ARNOLD S. JACKSON, M.D 271

INDEX TO ADVERTISERS . . . . . ADV. PAGE 38

Contents continued on page x

OWNERS AND PUBLISHERS
Philadelphia LEA & FEBIGER New York

COPYRIGHT, 1925, BY LEA & FEBIGER. ALL RIGHTS RESERVED. ENTERED AT THE POST-OFFICE AT PHILADELPHIA AS SECOND-CLASS MATTER
PUBLISHED MONTHLY. SUBSCRIPTION, SIX DOLLARS A YEAR, POSTPAID

INFANT DIET MEAD'S MATERIALS

CHOOSING AN INFANT'S DIET

If all babies were *alike* and *standardized*, then one food would probably take care of the nutritional requirements of most babies.

BUT—physicians know that foods must be altered to suit the nutritional requirements of each infant.

MEAD'S INFANT DIET MATERIALS are helping physicians to do *scientific* infant feeding.

The Mead Policy

Mead's Infant Diet Materials are advertised only to physicians. No feeding directions accompany trade packages. Information in regard to feeding is supplied to the mother by written instructions from her doctor, who changes the feedings from time to time to meet the nutritional requirements of the growing infant. Literature furnished only to physicians.

Mead's Dextri-Maltose (the carbohydrate of choice for modified cow's milk mixtures).

Mead's Casec (a useful adjunct when the baby is suffering from Fermentative Diarrhea).

Mead's Standardized Cod Liver Oil (as important to protect the infant from Rickets as orange juice protects from scurvy).

MEAD JOHNSON & COMPANY
EVANSVILLE, INDIANA, U. S. A.

THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

AUGUST, 1925

ORIGINAL ARTICLES.

A CONSIDERATION OF THE CLINICAL VALUE OF EPHEDRIN.*

WITH A REPORT ON ITS EFFECTS IN CERTAIN SPECIAL CASES.

BY T. GRIER MILLER, M.D.,

PHILADELPHIA.

(From the Medical Division of the University Hospital, University of Pennsylvania.)

I. **Introduction.** EPHEDRIN is the name given to an active principle isolated by Nagai[1] from an Asiatic drug, Ma Huang (Ephedra vulgaris var. helvetica), which has been used in the practice of medicine in China for more than five thousand years. In chemical composition it is closely allied to epinephrin and the recent comprehensive study of its physiological effects in animals and man by Chen and Schmidt[2] has showed that it is possessed of sympathomimetic actions to a conspicuous degree. It differs from epinephrin, however, in that the action of a single dose may persist for several hours, and it is reliably effective when given orally or by hypodermic injection.

The discovery of the physiological activity of extracts of the medulla of the suprarenal gland, the isolation from it of a cystalline principle possessing intense and characteristic power and the conception that this substance is a hormone which takes part in the normal adjustments of the organism to unusual strain and is supplied to it in varying amounts led to the hope and to the expectation that a new agent of unique power was available to the physician in the rational treatment of various bodily disorders. This hope and expectation have only partially been realized and important reasons

* This investigation has been made with the assistance of a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association.

are to be found in the evanescence of its action and in the uncertainty of its effects when given by other methods than that of intravenous injection.

The discovery of another substance, ephedrin, possessing a persistence of action many times greater than that of epinephrin and capable of effective utilization by either oral or hypodermic administration, may properly renew the hope of clinical effectiveness which the latter drug has not fulfilled. With this thought in mind, a supply of ephedrin having become available,* I have undertaken a study of its effects in selected patients in the University Hospital. Before describing the results a résumé of the known pharmacology of this drug may be useful.

II. **Résumé of the Pharmacology of Ephedrin** ($C_6H_5.CHOH.CH(CH_3)NHCH_3$). Mydriasis by ephedrin, with little change in accommodation or intraocular tension, was first observed by Miura[3]: rise of blood pressure and inhibition of intestinal movement by Amatsu and Kubota.[4] Chen and Schmidt showed that vasoconstriction and cardiac stimulation were responsible for the rise in blood pressure: they found that the uterus was stimulated and the bronchial muscle relaxed, and that during ephedrin mydriasis the pupillary light reflex was retained. The effects of a single intravenous injection persist for at least fifteen minutes and often much longer. To elicit similar effects by subcutaneous injection more than 10 times the intravenous dose is required. Effective absorption from the intestinal tract was proved.

The low toxicity of ephedrin was observed by Miura, by Chen and Schmidt and most recently by Chen.[5] The minimal lethal dose for rabbits, cats and dogs is from 30 to 100 times that required to produce conspicuous action. Daily administrations of large doses to rabbits for four weeks resulted neither in tolerance nor in detectable injury.

In the treatment of experimental shock in dogs, Chen showed restoration of the circulation by intravenous injection of 2 to 3 mg. per kg. Similar action was observed after hemorrhage.

Chen and Schmidt demonstrated rise of blood pressure in normal man following 60 mg. given subcutaneously or by mouth, with no untoward results: they also secured evidence of favorable action from a single dose in a patient in moderate surgical shock and from repeated doses in a patient with Addison's disease.

In one phase of its action on the circulation ephedrin differs from epinephrin: after repeated doses have been given to animals, further injections may be followed by lowering in blood pressure,

* The ephedrin used in this study was made in the laboratories of the Peking Union Medical College according to the method of K. K. Chen and under his supervision and was made available to me by the department of pharmacology of this University. I am indebted to Dr. Carl F. Schmidt of that department for much helpful advice during the course of these observations.

due, presumably, to depression of the heart. Intravenous injection of a large dose, therefore, in conditions of circulatory failure might be dangerous.

III. **General Observations.** Eighty-four acute clinical experiments have been made under controlled conditions; in other instances, the drug has been administered over long periods but without such careful supervision. Intelligent and coöperative patients were selected because a reliable account of subjective symptoms was desired in addition to the objective observations planned. Each acute experiment was made in the forenoon; the patient had breakfast before receiving the drug except in instances in which hourly urine collections were obtained; in those, breakfast was omitted. The majority of patients while under observation were kept quiet in bed; a few were seated in a chair, undisturbed as far as possible. Doses of ephedrin sulphate, ranging from 50 to 125 mg., were given orally or subcutaneously (in one case intravenously). Each patient was kept under close personal observation for a number of hours after administration of the drug.

The results obtained on this selected group of patients are summarized in Table I. The cases are arranged in descending order of the maximal increase in systolic blood pressure (ninth column). The data include sex, age, clinical diagnosis, dose of ephedrin and method of its administration, systolic blood pressure before the drug and highest reading after, the corresponding pulse rates, effects on heart as indicated by study of cardiac murmurs and certain special subjective and objective effects.

No definitely harmful effects occurred in any patient; a certain few complained, usually on being questioned, of palpitations or throbbings, of nervousness and rarely of a little nausea. Two vomited about ten hours after hypodermic injection; both were of a very nervous type and it is not certain that the ephedrin was causative. One who had evidence of marked myocardial degeneration showed a transient pulsus alternans about one hour after his injection. There were no other unfavorable phenomena and the patients did not object to taking the drug repeatedly; some felt distinctly stronger and better after receiving it. These observations agree with those of Chen and Schmidt concerning the slight toxicity of the drug.

(*a*) *Effects on Blood Pressure.* The most consistent results were obtained in reference to the systolic blood pressure. The observations were made at half- to one-hour intervals, and the maximal rise occurred within an hour when the dose was given subcutaneously and usually within two hours when the administration was oral. In the 84 instances, including only 2 presumably normal persons, some elevation occurred in 70; in 57 the rise amounted to 10 or more mm. of mercury, in 49 to 15 or more, in 37 to 20 or more, in 29 to 25 or more, in 21 to 30 or more and in

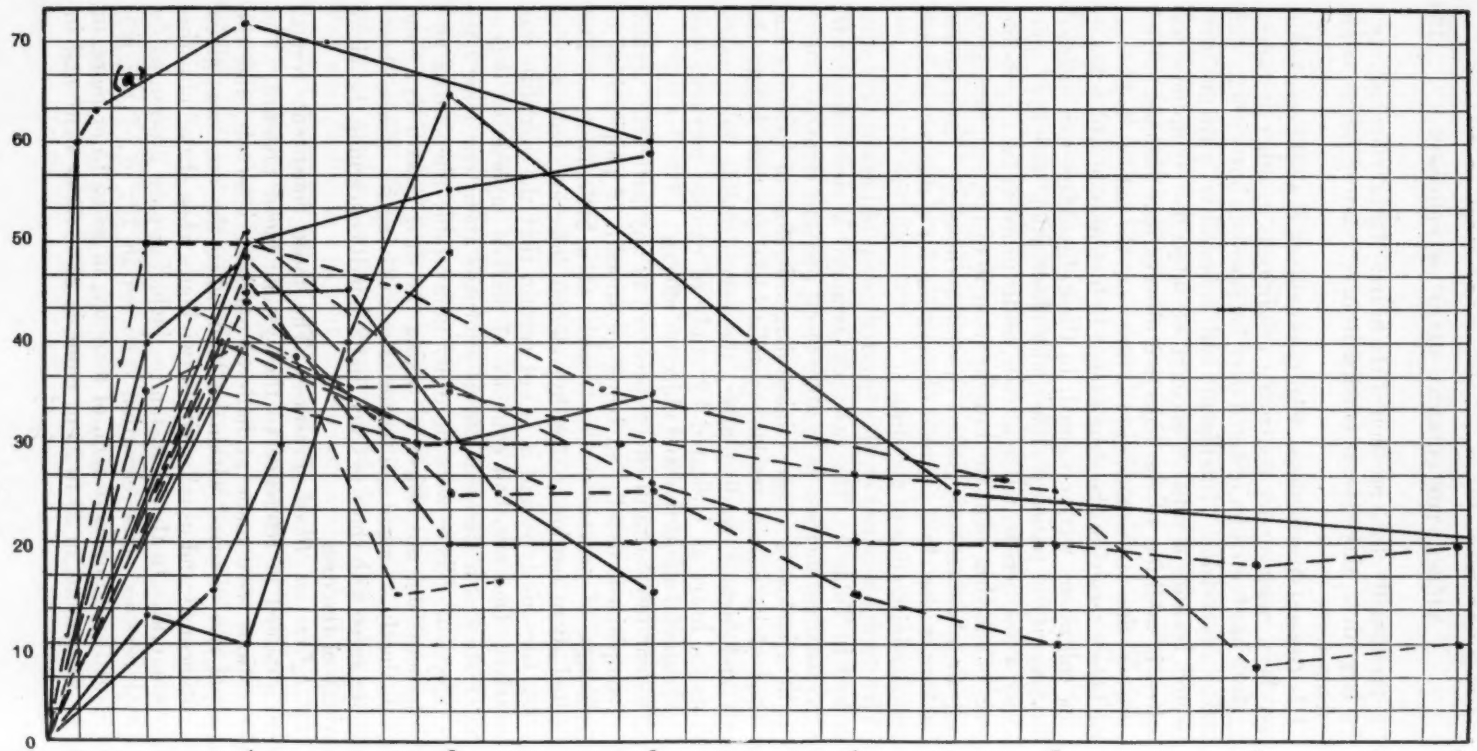

CHART I

15 to 40 or more. In 1 instance of acute peritonitis in which no pulse or blood pressure could be detected before giving the ephedrin a systolic pressure of 65 mm. and a diastolic of 50 mm. was obtained fifteen minutes after 100 mg. of the drug had been injected into a jugular vein. In 13 cases no rise occurred and in 6 of these there was an actual fall (the greatest drop amounting to 20 mm.). The clinical condition of these patients afforded no obvious explanation of this fall, but it is probable that the original level was unnaturally high because of their nervousness in the beginning of the experiment.

The duration of the systolic blood pressure rise varied: usually after reaching its highest point within one to two hours it slowly fell during the next three or more hours to the original level. In many instances, however, some elevation above the original level persisted after six or eight hours. Chart I shows the type of curve obtained.

This chart also shows that the extent of rise after oral administration is as marked as after subcutaneous injection, though, as stated, the action is somewhat more promptly elicited by the latter method. Of 69 cases (2 to 70) which showed increase in systolic pressure, 26 received the drug by mouth and 43 subcutaneously.

The diastolic pressures are not recorded, since they were not at all consistent, but it may be stated that they usually rose with the systolic though not to a comparable degree. Often they remained approximately the same throughout the experiment.

(*b*) *Effects on the Pulse Rate.* The pulse rates recorded were determined just before the ephedrin was given and at the time the maximal systolic bood pressure observation was made. The latter was not in every instance the lowest rate obtained but usually it was. In most cases there was strictly an inverse relation between these two phenomena, the pulse rate decreasing as the blood pressure rose, and the two came back to the original level at about the same time. This was not invariably true, however, and in 16 cases a definite increase in the pulse rate occurred. It is obvious that the direct stimulant effect of ephedrin on the cardiac accelerator mechanism is apt to be antagonized by the cardiac inhibitory action of increased blood pressure. In anesthetized animals, in which the vagus mechanism is depressed, the former action predominates; our observations indicate that in man the compensatory vagus effects are more apt to be encountered.

CHART I.—Curves of systolic blood pressure increase obtained on patients who showed a maximal rise of 30 or more mm. of mercury after the administration of ephedrin. The base line represents the level of blood pressure before ephedrin; the ordinates, therefore, show not the actual blood pressure, but the rise above the original level in mm. of mercury. The abscissas represent time intervals, the figures indicating hours. The solid lines were obtained after oral administration and the broken ones after subcutaneous injection. Curve (*a*) was obtained after intravenous administration. (See Case XIII.)

TABLE I.—GENERAL SUMMARY OF DATA OBTAINED IN REFERENCE TO 84 ACUTE CLINICAL EXPERIMENTS WITH EPHEDRIN. THE FOLLOWING ABBREVIATIONS ARE USED: IV. = INTRAVENEOUSLY; SC. = SUBCUTANEOUSLY; O. = ORALLY; INC. = INCREASED; DEV. = DEVELOPED; P. = PULMONIC AREA, AND A. = AORTIC AREA.

No.	Sex.	Age.	Clinical diagnosis.	Ephedrin administered.		Systolic blood pressure in mm. Hg.			Pulse rate.		Systolic murmurs.	Special effects.
				Amount in mg.	Method.	Before.	After.	Maximal increase.	Before.	After.		
1	M.	42	Acute peritonitis	100	Iv.	?	65	65	140	132	None	Heart sounds became clearly audible. Died 12 hours later.
2	F.	39	Neurasthenia	100	0	115	125	65	80	64	Inc. at apex, dev. at base	Nervous. Heart sounds louder.
3	M.	22	Arthritis deformans	100	0	100	158	58	68	80	Dev. at all areas	Vital capacity increased 50 cc.
4	M.	16	Convalescent pneumonia	100	Sc.	115	165	50	66	66	Dev. at P. and apex	Nervous.
5	M.	18	Gonorrheal arthritis	100	Sc.	95	145	50	52	52	.....	Blood sugar not affected.
6	M.	32	Duodenal ulcer	100	Sc.	110	160	50	60	60	Dev. at P.	None observed.
7	M.	30	Duodenal ulcer	100	0	92	140	48	74	60	Inc. at apex	Nervous and vomited.
8	M.	40	Pleurisy	100	Sc.	95	140	45	72	60	Dev. at base	None observed.
9	M.	24	Aortic regurgitation	100	Sc.	125	170	45	84	62	Inc. at base and apex	No symptoms, but developed cardiac arthythmia 6 hours later.
10	M.	19	Diabetes	100	0	115	160	45	64	62	Dev. at P. and apex	Basal metabolism increased.
11	M.	30	Duodenal ulcer	90	Sc.	105	145	40	80	60		
12	M.	30	Duodenal ulcer	100	0	95	135	40	92	84	Inc. at A.	Fluoroscope showed marked ventricular pulsations.
13	M.	26	Acute rheumatic fever	100	Sc.	115	155	40	68	64	Dev. at all areas	Palpitations.
14	M.	21	Gastric neurosis	100	0	95	135	40	60	54	Dev. at all areas	Vital capacity unchanged. Felt better and stronger. Slight throbbing throughout body. Basal metabolism increased.
15	F.	43	Pyonephrosis	100	Sc.	90	130	40	..	..	.....	Urine output increased.
16	M.	30	Duodenal ulcer	100	Sc.	100	135	35	76	64		
17	M.	14	Rheumatic valvulitis	100	Sc.	116	150	34	88	60	Inc. at all areas; diast. at base inc.	Heart sounds stronger. Slight palpitation. Spots of erythema

15	F.	43	Pyonephrosis	100	Sc.	90	130	40	..	..	.....	throbbing throughout body. Basal metabolism increased.
16	M.	30	Duodenal ulcer	100	Sc.	100	135	35	76	64		Urine output increased.
17	M.	14	Rheumatic valvulitis	100	Sc.	116	150	34	88	60	Inc. at all areas; diast. at base inc.	Heart sounds stronger. Slight palpitation. Spots of erythema over anterior chest.
18	M.	60	Cerebral thrombosis	50	Sc.	130	160	30	72	66	No change	Slight headache. Heart sounds irregular in force.
19	M.	35	Normal	100	Sc.	110	140	30	60	60	Dev. at apex	Slight headache, urinary output increased, slight albuminuria.
20	M.	14	Rheumatic valvulitis	100	Sc.	115	145	30	68	60	Inc. at all areas; diast. at base inc.	
21	M.	21	Gastric neurosis	100	0	95	125	30	60	60	Dev. at all areas.	
22	M.	22	Rheumatic fever	50	0	95	124	29	64	76	Inc. at all areas, dev. diast. at base	Nervous after 4 hours.
23	F.	16	Gastric neurosis	100	0	105	132	27	72	72	Dev. at all areas	None observed.
24	M.	36	Addison's disease	100	0	84	110	26	88	112	None	Comfortable.
25	M.	61	Gastric neurosis	75	Sc.	120	145	25	92	68	Dev. at A. and apex	Fluoroscope showed marked ventricular pulsations. Nervous.
26	M.	64	Prostatic hypertrophy and myocarditis	50	0	95	120	25	90	86	.....	Heart sounds stronger. Hiccough of a week's duration ceased on second day. General condition improved.
27	M.	35	Pyloric stenosis	100	Sc.	105	130	25	88	96	None	Felt better.
28	M.	22	Rheumatic fever	60	Sc.	115	140	25	92	100	Inc. at all areas, dev. diast. at base	Palpitations few minutes after injection.
29	M.	11	Diabetes	60	Sc.	108	130	25	96	72	Dev. at P. and apex	None observed.
30	M.	36	Addison's disease	100	Sc.	75	98	23	92	108	.....	Nervous after one hour.
31	M.	11	Diabetes	60	Sc.	108	130	22	96	72	Dev. at P. and apex	None observed.
32	F.	29	Addison's disease	75	Sc.	90	112	22	80	68	None	Heart sounds stronger. Not consciously disturbed.
33	M.	61	Gastric neurosis	100	Sc.	140	162	22	60	60	Dev. at all areas	Gastrointestinal roentgen-ray study showed no unusual features. Thumping in chest.
34	F.	41	Arthritis deformans	100	0	90	110	20	88	88	Dev. at P.	Skin moist.
35	M.	71	Heart block	100	Sc.	90	110	20	40	58	None.	Electrocardiograms showed increase in ventricular rate.

TABLE I.—GENERAL SUMMARY OF DATA OBTAINED IN REFERENCE TO 84 ACUTE CLINICAL EXPERIMENTS WITH EPHEDRIN. THE FOLLOWING ABBREVIATIONS ARE USED: IV. = INTRAVENEOUSLY; SC. = SUBCUTANEOUSLY; O. = ORALLY; INC. = INCREASED; DEV. = DEVELOPED; P. = PULMONIC AREA, AND A. = AORTIC AREA.—(*Continued.*)

No.	Sex.	Age.	Clinical diagnosis.	Ephedrin administered.		Systolic blood pressure in mm. Hg.			Pulse rate.		Systolic murmurs.	Special effects.
				Amount in mg.	Method.	Before.	After.	Maximal increase.	Before.	After.		
36	M.	11	Diabetes	100	0	100	120	20	72	68	Dev. at A.	Urine increased.
37	M.	14	Pneumothorax	50	Sc.	100	120	20	120	128	None	None observed.
38	F.	29	Addison's disease	100	0	90	108	18	100	90	None	None observed at time but nervous and vomited after 10 to 12 hours.
39	M.	36	Addison's disease	100	0	75	92	17	88	92	None	None observed.
40	M.	64	Chronic myocardial disease	75	Sc.	145	160	15	100	112		
41	F.	35	Endocrine disease	90	Sc.	95	110	15	88	108	None	Heart sounds louder.
42	M.	19	Convalescent pneumonia	100	Sc.	115	130	15	100	72	Inc. at all areas	Slight palpitation.
43	M.	14	Convalescent pneumonia	100	0	100	115	15	116	112	Dev. at apex	Vital capacity increased 150 cc.
44	M.	29	Retroperitoneal sarcoma	100	0	115	130	15	74	64	Dev. at P.	Heart sounds stronger. Vomited but not certainly due to drug.
45	F.	29	Addison's disease	100	Sc.	90	105	15	84	68	None	Blood sugar and blood calcium not definitely affected.
46	M.	39	Syphilitic endocarditis	100	Sc.	120	135	15	98	100	Inc. at all areas, diast. at base inc.	
47	M.	39	Normal	100	Sc.	115	130	15	80	72	Dev. at apex	Throbbing in head, nervous, no effect on urinary output but albuminuria.
48	M.	60	Cerebral thrombosis	100	Sc.	135	150	15	84	88	No change	Comfortable but pulsus alternans developed.
49	M.	30	Duodenal ulcer	100	0	105	120	15	100	88		
50	M.	22	Neurasthenia	100	0	110	124	14	72	100	Inc. at all areas	Nervous and weak.
51	M.	36	Pneumonia	50	0	115	128	13	124	124	None	None observed.
52	M.	60	Asthma	100	Sc.	110	122	12	88	88	No change	No effect on urinary output.

48	M.	60	Cerebral thrombosis	100	Sc.	135	150	15	84	88	No change	Comfortable but pulsus alternans developed.
49	M.	30	Duodenal ulcer	100	0	105	120	15	100	88		
50	M.	22	Neurasthenia	100	0	110	124	14	72	100	Inc. at all areas	Nervous and weak.
51	M.	36	Pneumonia	50	0	115	128	13	124	124	None	None observed.
52	M.	60	Asthma	100	Sc.	110	122	12	88	88	No change	No effect on urinary output.
53	F.	16	Gastric neurosis	75	0	120	132	12	80	68	Dev. at all areas	Fluoroscope showed increased ventricular pulsations. Urine not increased
54	F.	29	Neurasthenia	100	0	115	125	10	88	80	Inc. at all areas	None observed.
55	M.	29	Arthritis deformans	1 cc adrenalin	Sc.	130	140	10	92	92	Dev. at all areas	Slight palpitation.
56	M.	36	Pneumonia	75	Sc.	105	115	10	64	72	Dev. at P.	Heart sounds stronger.
57	M.	65	Asthma	100	Sc.	110	120	10	88	88	No change.	Heart sounds irregular in force and few extra systoles. More comfortable.
58	M.	65	Asthma	50-6th hour	Sc.	..	..	..	..	..	.....	No definite sustained improvement after 10 days.
59	M.	13	Diabetes	100	Sc.	110	118	8	98	100	None	Increase in amount of urine.
60	M.	26	Gastric neurosis	100	0	95	100	5	68	70	None	No effect on urinary output.
61	F.	22	Urticaria	100	0	80	95	5	..	..	None	Itching relieved. No obvious effect on lesions.
62	M.	60	Cerebral thrombosis	50	Sc.	120	125	5	76	68	No change	None observed.
63	F.	41	Arthritis deformans	50	0	100	105	5	92	104	None	None observed.
64	M.	61	Gastric neurosis	100	Sc.	140	162	5	60	60	Dev. at all areas	Gastrointestinal roentgen-ray study showed no unusual features. Thumping in chest.
65	F.	38	Addison's disease	125	Sc.	90	95	5	80	80	None	Slight dizziness.
66	M.	36	Aortic regurgitation	100	0	120	125	5	96	96	Diast. at base unchanged	None observed.
67	M.	65	Asthma	50	Sc.	120	124	4	104	100	No change	Felt better. Wheezing less and cough looser.
68	M.	38	Asthma	100	Sc.	92	95	3	118	110	None	More comfortable for 2 to 3 hours.
69	M.	44	Luetic myocarditis with fibrillation	50	Sc.	110	112	2	80	68	No change	None observed.
70	F.	29	Neurasthenia	100	Sc.	118	120	2	94	76	Inc. at all areas	Hands cold and moist.
71	M.	13	Rheumatic fever	50	0	100	100	0	74	80	No change	None observed.

TABLE I.—GENERAL SUMMARY OF DATA OBTAINED IN RFERENCE TO 84 ACUTE CLINICAL EXPERIMENTS WITH EPHEDRIN. THE FOLLOWING ABBREVIATIONS ARE USED: IV. = INTRAVENOUSLY; SC. = SUBCUTANEOUSLY; O = ORALLY; INC. = INCREASED; DEV. = DEVELOPED; P. = PULMONIC AREA, AND A. = AORTIC AREA.—(*Continued.*)

No.	Sex.	Age.	Clinical diagnosis.	Ephedrin administered.		Systolic blood pressure in mm. Hg.			Pulse rate		Systolic murmurs.	Special effects.
				Amount in mg.	Method.	Before.	After.	Maximal increase.	Before.	After.		
72	F.	34	Toxic adenoma of thyroid	100	0	135	135	0	128	128	Dev. at A.	Nervous.
73	M.	39	Syphilitic endocarditis	50	Sc.	170	170	0	80	84	No effect on diast. at base	None observed.
74	M.	50	Lymphosarcoma of neck	50	Sc.	120	120	0	88	84	No change.	None observed.
75	M.	60	Asthma	100	0	105	105	0	80	90	No change	Quite comfortable. Slight decrease in urinary output.
76	M.	36	Aortic regurgitation	100	0	115	115	0	88	96	No change	No effect on urinary output.
77	F.	39	Neurasthenia	75	0	130	130	0	80	100	.....	Slight increase in urinary output.
78	M.	15	Pneumonia	60	Sc.	110	105	− 5	112	100	None	None observed. Fell asleep.
79	M.	65	Asthma	100	Sc.	120	110	−10	92	92	No change	Heart sounds irregular in force. Wheezing less. Felt better.
80	M.	50	Lymphosarcoma of neck	75	Sc.	120	110	−10	86	94	.....	Heart sounds louder. Sense of constriction in upper chest.
81	F.	46	Asthma	100	Sc.	132	120	−12	..	..	No change	Attack relieved, some rales persisted.
82	M.	60	Asthma	50	Sc.	120	105	−15	108	100	No change	Felt better. Slight tremor. Breathing easier.
83	M.	60	Asthma	50–6th hour	..	..	..	..	..	..	No change	Definite improvement which was maintained.
84	M.	22	Gonorrheal arthritis	100	Sc.	110	90	−20	96	100	.....	Blood sugar not affected.

(*c*) *Effects on Heart Action.* It was found by Chen and Schmidt, using the myocardiograph, that in dogs and cats the amplitude of the cardiac contractions is increased by ephedrin, due to stimulation of the cardiac accelerator ganglia plus stimulation of the terminals of the sympathetic nerve fibers in the heart muscle. That a similar effect is produced in man is evidenced by the observation of 3 of the patients under the fluoroscope before and after administering the drug. The excursion of the ventricular and also the aortic shadows was greater after the ephedrin had been given (observations by Dr. Eugene Pendergrass). This action was also indicated by a more forceful apex impulse which could be seen and felt, and by an increased loudness of the heart sounds. In addition it is suggested that the palpitations which were sometimes complained of may have been due to such an increase in amplitude and perhaps strength of the cardiac contractions.

An interesting finding in this connection was the development or intensification of systolic heart murmurs while the patients were under the influence of the drug. These sometimes developed at the apex alone, again at the base alone, either aortic or pulmonary area, and in other instances at all these areas. In 1 case in which 1 cc of 1 to 1000 epinephrin chlorid solution was given subcutaneously similar systolic murmurs were produced. It is important to note that these murmurs sometimes developed when the increase in systolic pressure was only slight or moderate. The explanation is not clear, but it is suggested that the basal ones may be due to a relative stenosis of the aortic and pulmonary valves resulting from unusual distension of the two great arteries at the beginning of systole and that the apical one may be due to relative insufficiency of the mitral valve from a similar distension of the heart cavities. Thayer[6] has given such an explanation for the common functional systolic murmurs. Furthermore, it fits in well with the fluoroscopic evidence of increased contraction in systole and distention in diastole. This matter deserves further investigation.

(*d*) *Effects on Urinary Secretion.* In Table II are collected the hourly outputs of urine in 25 patients who were observed for five hours or more. Twenty-two of them were given ephedrin and the other 3 were used as controls. In each instance the bladder was emptied at 7 o'clock in the morning, nothing having been taken by mouth since the previous evening, and subsequently collections were made at hourly intervals until noon. In all but 1 case (No. 19) 100 cc of water were given at 7, 8, 9, 10 and 11 o'clock: in that single instance 150 cc were so given. At 9 o'clock after the second hourly collection the ephedrin was administered. The first 2 specimens, therefore, represented the output without the drug and the next 3 the output while the individuals were under its influence. Averages from these two groups were made and their relation is expressed in the ratio column. From these ratios it will be observed that the

TABLE II.—SUMMARY OF DATA ON THE EFFECT OF EPHEDRIN ON THE SECRETION AND CHARACTER OF THE URINARY OUTPUT IN 25 CASES.

No.	Sex.	Age.	Diagnosis.	Ephedrin.		Maximal systolic blood pressure increase in mm. Hg.	Urinary output.					Ratio between the hourly average before and after ephedrin.	Maximal albumin 1–6 hours after ephedrin.
				Amount in mg.	Method of administration		7 to 8 A.M.	At 9 A.M.	At 10 A.M.	At 11 A.M.	At noon.		
3	M.	22	Arthritis deformans	100	0	58	25	45	50	30	90	10:16	○
4	M.	16	Convalescent pneumonia	100	Sc.	50	60	70	...	...	150	10:8	++
8	M.	40	Pleurisy	100	Sc.	45	110	110	50	60	40	10:5	+++
9	M.	24	Aortic regurgitation	100	Sc.	45	200	170	110	220	250	10:10	+++
10	M.	19	Diabetes	100	0	45	90	310	225	310	150	10:12	++
14	M.	21	Gastric neurosis	100	0	40	30	60	50	20	60	10:10	+++
19	M.	35	Normal	100	Sc.	30	130	140	305	102	500	10:22	+
29	M.	11	Diabetes	100	0	22	50	50	150	250	150	10:36	++
37	M.	14	Convalescent pneumonia	100	0	20	60	20	180	50	85	10:24	+++
44	M.	29	Retroperitoneal sarcoma	100	0	15	60	60	80	50	80	10:11	

45	F.	29	Addison's disease	100	0	15	45	48	60	60	100	10:16	
47	M.	39	Normal	100	Sc.	15	32	20	22	21	24	10:8	+++
49	M.	30	Duodenal ulcer	90	Sc.	15	50	145	350	150	100	10:20	
52	M.	60	Asthma	100	Sc.	12	70	60	60	60	50	10:9	○
53	F.	16	Gastric neurosis	75	0	12	25	30	20	20	20	10:8	
59	M.	13	Diabetes	100	Sc.	8	12	70	160	340	200	10:57	
60	M.	26	Gastric neurosis	100	0	5	50	50	50	45	46	10:9	
64	M.	61	Gastric neurosis	75	0	5	50	50	150	200	100	10:30	+++
66	M.	36	Aortic regurgitation	100	0	5	100	120	110	75	90	10:8	
75	M.	60	Asthma	100	0	0	90	50	30	50	50	10:6	
76	M.	36	Aortic regurgitation	100	0	0	90	80	80	48	45	10:7	
77	F.	39	Neurasthenia	75	0	0	15	15	20	25	30	10:17	○
Controls	F.	16	Gastric neurosis	None	...	...	25	20	25	25	25	10:11	
	M.	61	Gastric neurosis	None	...	...	60	25	50	50	40	10:11	
	M.	40	Pleurisy	None	...	...	60	60	50	70	60	10:10	

results are conflicting and not at all in agreement with the effect on blood pressure, as was expected. Usually there was an increase in output and this was very marked in some, especially in two diabetics (Nos. 29 and 59), yet another diabetic (No. 10) showed a ratio of only 10 to 12. In 2 instances (Nos. 19 and 47) the experiment was continued over a period of ten hours but with different results, one showing a decided diuresis (10 to 22) and the other a slight decrease (10 to 8) for the three-hour period immediately following the injection. The later collections were the average ones for the pre-ephedrin period. In connection with these 2 individuals, both of whom were presumably normal, it is interesting that one averaged only 26 cc of urine per hour on 100 cc of water while the other put out an average of 135 cc hourly on an intake of 150 cc on the three controls (Nos. 74, 75 and 76) the ratio showed no difference between the outputs in the two periods.

These varying results lead to no definite conclusion, but seem to show a tendency to diuresis after ephedrin administration. The work of Chen and Schmidt indicated that the drug caused first a decrease in output from renal vasoconstriction and that this was followed by a diuresis incident to a secondary vasodilatation while the general blood pressure was still elevated. The differences in the effects on the urinary secretion might, therefore, be due to variation in the relation between the ephedrin effect on the general blood pressure and on the renal vascular apparatus.

It has been suggested that there might be in addition some renal irritation which aided in the diuresis. This thought was based on a single observation by Chen and Schmidt in a rabbit which showed a diuresis with intermittent glycosuria and albuminuria after excessive intravenous doses daily for nine days. In spite of perfect health and a gain in weight during the next twelve days, it showed at the end of that time, when killed, some degenerative changes in the convoluted tubules. Rabbits, however, frequently develop tubular lesions spontaneously, and a single case of such a change in a rabbit is, therefore, of no significance. Furthermore, in all the clinical cases that have been studied no evidence of disturbance in either the quantity or the character of the urine lasting longer than a few hours has been observed.

A consideration of the influence of the drug on the character of the urine is not to be dealt with extensively here, in as much as Dr. Isaac Starr expects to report on this separately, but the last column in Table II, supplied by him, shows some albuminuria for a few hours after ephedrin in most of those patients who had a decided increase in blood pressure. This again does not prove renal irritation, for work recently accomplished in the laboratory of pharmacology of this university indicates strongly that transient albuminuria may result from the renal vasconstriction produced by epinephrin (and presumably by other substances of the same type),

not because of a direct damaging action upon renal tissue but because of transient cessations of circulation through the blood-vessels of such duration as to cause the alterations in permeability characteristic of asphyxia.

(*e*) *Effects on the Basal Metabolism and Blood Sugar.* Basal metabolism studies before and after the administration of ephedrin are being made by Dr. Leon Jonas and the writer. These also will be reported separately but the following table is given to show the decided increase that has occurred in 2 of 4 cases. The same investigators are studying the blood sugar effects, but as yet have got entirely negative results.

TABLE III.—EFFECT OF EPHEDRIN ON THE BASAL METABOLISM IN 4 CASES.

No.	Sex.	Age.	Amount of ephedrin administered subcutaneously.	Maximal systolic blood pressure increase.	Basal metabolism before, and a half hour after ephedrin.	
					Before.	After.
9 . .	M	24	100 mg.	45	+6	+21
10 . .	M	19	100 mg.	45	−15	+7
85 . .	F	27	100 mg.	25	−7	+2.3
24 . .	M	36	125 mg.	20	+4	+9

IV. **Special Clinical Observations.** The following cases are reported to show in greater detail the results obtained from the therapeutic use of ephedrin in certain types of disease in which, on account of its physiological actions, there was reason to believe that this drug might be of practical value. It is appreciated that the number of cases in each group is too small to justify final conclusions but it is felt that they are of sufficient significance to be reported and that they warrant further studies in such and other clinical conditions.

A. Addison's Disease. It could hardly be expected that any drug would serve as a cure for a disease that is dependent upon extensive destructive change in such important glands of internal secretion as the adrenals. Furthermore, it is known that injections of epinephrin itself have had little or no influence on the symptoms or course of Addison's disease. Yet it is appreciated that it has been impossible practically to produce an epinephrin effect continuously in patients because of its brief action and the necessity of giving it hypodermically. These practical objections being overcome in ephedrin, which has similar physiological actions, it seemed worth while, and especially so in view of Chen and Schmidt's encouraging report in a single case, to try it out in other cases of Addison's disease with the hope that at least in the early ones it might compensate to some extent for the deficiency in adrenal function. The results are not highly encouraging but do seem to

suggest that at least temporary benefit may be expected in some cases.

Case Reports. CASE I.—A married woman, aged twenty-nine years, a private patient, was admitted to the University Hospital on October 16, 1924, complaining of weakness, loss of weight and a brownish discoloration of the skin. She had been losing weight for five months (170 down to 126 pounds). The brownish tint of the skin had developed insidiously, being first noted under the eyes and under the chin. When I first saw her, the whole skin surface seemed somewhat discolored, and especially was this marked over the face, arms, hands, back and upper anterior chest. There were definite discolorations of the flexor and extensor surfaces of the joints and of the umbilicus and nipples. There were also spots of blackish pigmentation along the dorsum of the tongue. The vagina showed brownish-black spots. The heart and lungs were negative to physical examination and no signs of gastrointestinal disease could be found. The blood pressure was 90 systolic and 65 diastolic. The blood counts and urinalyses were negative. A roentgenological examination of the chest was negative except for some calcified glands about the root of right lung. Other laboratory examinations, including a roentgenological study of the gastrointestinal tract, gastric analysis, feces examination and a van den Bergh test were negative. A von Pirquet test was positive. A blood-sugar tolerance test showed a quick response with a secondary drop to an unusually low level (49 mg. after one and a half hours).

On an inital dose of 50 mg. of ephedrin hypodermically her systolic blood pressure rose from 92 to 105 mm. of mercury and her pulse rate dropped from 72 to 50. No change in the blood-sugar level occurred (see Table IV).

TABLE IV.—EFFECT OF 50 MG. EPHEDRIN, GIVEN SUBCUTANEOUSLY, ON BLOOD PRESSURE, PULSE RATE AND BLOOD SUGAR LEVEL IN A CASE OF ADDISON'S DISEASE. DRUG GIVEN AT 9 A.M.

	Time of day.					
	9 A. M.	9.30 A.M.	10 A. M.	10.30 A. M.	11 A. M.	11.30 A. M.
Blood pressure in mm. Hg.	92/60	100/65	105/65	103/65	106/65	100/65
Pulse rate	72	60	50	54	56	60
Blood sugar in mg. per 100 cc	85	86	84	85	84	

After each of several similar doses of ephedrin given both orally and hypodermically she complained of some nervousness, a feeling

of excitement or apprehension, and a few times a little tremor of the hands was noted. The dose was therefore reduced to 25 mg. three times a day and on this she was discharged from the hospital to her home in another part of the state. The supply of the drug lasted only two or three weeks longer but during that time she improved in strength considerably and was able to take up her work again. Then, without the medicine, her weakness returned. From January 25 to February 10, on 30-mg. doses three times a day she again showed symptomatic improvement, but by February 24 her weight had dropped to 111 pounds and her general condition was no better. Then several acute experiments with ephedrin were made. It was found that a hypodermic dose of 75 mg. raised the systolic pressure from 90 to 110 mm. of mercury and did not disturb the patient so much as the 50 mg. doses had done before. On 100 mg. her blood sugar was not affected; neither was her blood calcium or phosphorus. After that, she took the medicine only for a period of ten days, because of our inability to furnish it, but during that time she gained 4 pounds in weight, felt better and was able to be out of doors and reasonably active. On April 14, she weighed only 105 pounds and her blood pressure was 95 systolic and 65 diastolic. Again she was started on 50-mg. doses orally three times a day. This soon caused nausea and vomiting and had to be abandoned.

The symptomatic improvement during the short periods when ephedrin was being given and the gain in weight over one period of ten days as well as the positive increase in blood pressure for three to five hours after single doses indicate that it was of at least temporary value in this case. It is hoped that by using smaller doses in the future the patient's unfavorable reactions may be avoided and that she may be kept continuously under its influence.

CASE II.—A man aged thirty-six years, was admitted to the University Hospital with a history of attacks of weakness and gradually increasing skin discoloration over a period of five years. His skin generally and the entire mucous membrane of his mouth showed a marked brownish-black hue and his blood pressure was consistently low. There were no demonstrable visceral lesions. After careful study the diagnosis of Addison's disease was made and ephedrin studies were undertaken. On a dose of 100 mg., given subcutaneously, his blood pressure did not vary over a period of one hour, remaining at 80 systolic and 50 diastolic. His pulse rate increased from 84 to 100. A few days later with a similar dose the blood pressure went from 75 systolic and 50 diastolic to 90 systolic and 50 diastolic in thirty minutes and after three hours was 98 systolic and 50 diastolic, the pulse rate having risen from 92 to 108. Again on an oral dose of 100 mg., after having taken it routinely in 50-mg. doses three times a day for a week, the pressure

rose from 75 systolic and 55 diastolic to 92 systolic and 60 diastolic in two hours and after a slight exertion three hours later it went to 115 systolic and 75 diastolic. Then the ephedrin was omitted for thirty-six hours when 125 mg. were given subcutaneously, this causing a rise from 72 systolic and 55 diastolic to 92 systolic and 55 diastolic in thirty minutes and an increase in the pulse rate from 84 to 100. His basal metabolism before this dose of ephedrin was +4 and thirty minutes afterward it was +9. Two days later, the patient having received none of the drug in the interval, he developed an acute respiratory infection and died within twenty-four hours.

This patient had no disagreeable sensations from his doses of ephedrin, got a moderate increase in his blood pressure after each administration and was feeling stronger and better so long as it was kept up.

B. Asthma. In a single experiment on a pithed dog, after an injection of physostigmin had produced marked bronchial spasm, Chen and Schmidt secured prompt dilatation of the bronchi by ephedrin, though the effect was not well sustained and subsequent doses did not cause dilatation even when epinephrin continued to be effective. They had no opportunity to try the drug clinically, but they expected that beneficial results might be obtained. The following case reports are, therefore, of interest and seem to indicate that ephedrin does often have a relaxing influence on the bronchial spasm of asthma though this cannot be counted upon in every case and it is perhaps never as complete as that obtained from epinephrin.

CASE III.—A woman, aged sixty-six years, had suffered from an allergic type of hay fever and asthma for eighteen years. On admission to the wards of the hospital she was intensely dyspneic and cyanosed and had typical asthmatic breathing. She was relieved by injections of epinephrin several times and then put on 50-mg. doses of ephedrin by mouth four times a day. Subsequently she showed considerable improvement, although occasionally she still presented slight wheezing and once the intern gave another injection of epinephrin for a moderately severe attack during the night. On another such occasion an extra dose of 100 mg. of ephedrin by mouth gave definite relief. After that she was given 100 mg. orally four times a day and required in addition only an occasional hypodermic of epinephrin. This patient's blood pressure was carefully followed at half-hour intervals after one 50-mg. oral dose and after several 100 mg. subcutaneous doses of ephedrin. Neither the systolic nor diastolic pressure varied appreciably, indeed sometimes decreased, and yet she felt more comfortable for about three hours after these doses and her wheezing was considerably reduced.

In a personal communication Dr. Alfred Stengel gives the follow-

ing data on two of his private patients with asthma to whom he had given ephedrin.

CASE IV.—"Mrs. P., aged sixty-five years, has had asthmatic attacks for eighteen years. Under medical treatment she at one time was relieved for a period of a year, but with this exception, has suffered rather constantly. There has been some intranasal trouble and a good deal of tonsillitis; latterly, she has arthritic changes in her fingers. On examination, I found considerable evidence of sclerosis and some hypertension. The heart was not enlarged, but there was a soft systolic murmur over the arch and an accentuated second sound; lungs definitely emphysematous and musical rales everywhere. She improved somewhat under medical treatment (potassium iodid, extract of opium, digitalis and hyoscyamus), but was not very thoroughly relieved. On April 10, I gave her some of the ephedrin capsules (50 mg.) and told her to take them twice daily. She has since been in on two occasions reporting a remarkable relief from her asthmatic attacks. How much this may be due to the capsules, and how much to the capsules of cerium oxalate, digitan and belladonna that I had asked her to take at the same time, I can hardly say."

CASE V.—"Mr. J. B. C., aged fifty-three years, began to suffer with asthmatic symptoms at about thirty-six years of age, and continued for several years. He has not had in recent years any severe attacks, but early in 1925 he consulted me on account of asthmatic breathing, and stated that he had been troubled a little for several years past. During the winter of 1924–25, after a coryza and more general upper respiratory infection, marked asthmatic symptoms occurred. Various sorts of medical treatment were more or less unavailing. In May, he began the use of ephedrin, taking 2 or 3 doses (50 mg.) daily and an occasional extra dose for the paroxysms. This had an immediate effect in reducing the violence of his paroxysms and soon made the further use of epinephrin injections unnecessary. According to reports to me, the effect of the ephedrin was very striking and unmistakable. Just before sailing for Europe on June 24, he reported that his asthma had practically ceased and that he had used but 1 capsule of ephedrin for some time past."

CASE VI.—Dr. Richard A. Kern reported to me the case of a woman, aged fifty-four years, who had had pollen asthma and hay fever for twenty years. She had been getting 2 to 6 hypodermics of epinephrin daily. During one period of four days, on two to five 50-mg. capsules of ephedrin by mouth, no hypodermics were required, but subsequently she became nauseated from the capsules and returned to the hypodermics. Later on only 2 capsules of

ephedrin a day and 2 hypodermics of epinephrin her condition remained very good for five days of observation. There was no significant change in her blood pressure at any time.

CASE VII.—M. J. K., a patient of Dr. S. Paul Taylor of Altoona, Pennsylvania, who had suffered from severe asthmatic attacks irregularly for twenty years, was finally able to get relief only from 20 to 25 minim doses of epinephrin chlorid and this relief was far from complete. He was getting 4 such doses daily when I first saw him with Dr. Taylor. Physical examination was negative but for the signs of emphysema with asthma. Roentgenological examination of the chest suggested some bronchiectasis and bronchoscopic study by Dr. R. M. Lukens showed a chronic tracheobronchitis with a little blood-tinged pus coming from the left lower lobe bronchus. He was started on three 30-mg. capsules of ephedrin daily and later they were given as frequently as every two hours but no relief from his dyspnea ensued. On the more frequent doses he complained of "levitation, light headedness, fluttering in the chest, perspiration and an enlarged head."

In this case of severe asthma no benefit was derived from ephedrin although it was given to the point of producing toxic symptoms.

CASES VIII and IX.—Two men, sixty-five and sixty years of age respectively, had suffered from asthma for many years and both had associated emphysema with myocardial degeneration. Neither showed any marked blood-pressure increase after 50 to 100 mg. doses of ephedrin, given orally or subcutaneously, and on several occasions there was a drop in the systolic blood pressure within one to two hours after its administration. Both, however, got a certain amount of symptomatic relief for two to four hours after its use and often the cough was looser and more productive. There was also noted some decrease in the intensity of the wheezing breath sounds. At other times there seemed to be no effect on the physical signs.

These 2 patients were put on 50-mg. doses orally three times a day continuously for several weeks. One showed only slight improvement. This patient had been relieved by epinephrin injections when first admitted to the hospital, but at the time the ephedrin administrations were begun even 1-cc doses of 1 to 1000 epinephrin chlorid gave only slight relief. The other patient still got relief from epinephrin for thirty to sixty minutes, but after the ephedrin was begun he only occasionally required the hypodermics of epinephrin.

C. Other Allergic Conditions. CASE X.—A patient, a young married woman, on the private service of Dr. Alfred Stengel, having a pleurisy with effusion, developed acute urticarial lesions involving the entire body surface. An injection of 5 minims of 1 to 1000 epinephrin chlorid gave relief from the intense itching and an oral

dose of 50 mg. of ephedrin and of 50 mg. of luminal one hour later kept her sufficiently comfortable to sleep for ten hours. Then the itching returned and was not definitely affected within an hour by a second dose of 50 mg. of ephedrin, but after another dose of the same amount there was distinct relief. Within an hour after the last dose the blood pressure rose from 85 systolic and 60 diastolic to 95 systolic and 60 diastolic. Subsequently 100-mg. doses were given by mouth approximately every six hours and each time there was relief from the subjective symptoms for four to six hours. The lesions themselves were not objectively affected and did not disappear until the fourth day. At no time were any disagreeable effects from the ephedrin experienced.

CASE XI.—A boy, aged fourteen years, developed a generalized urticaria one week after a prophylactic dose of antitetanic serum. An injection of 5 minims of 1 to 1000 epinephrin chlorid solution gave complete relief for an hour or more and subsequently he was kept reasonably comfortable by 50-mg. doses of ephedrin orally four times a day. At one time during the second day his subjective symptoms were almost as marked as in the beginning and an extra dose of ephedrin at that time (three hours after the last regular dose) caused a disappearance of the lesions and the itchiness within thirty to sixty minutes.

D. Circulatory Disturbances. The predominant action of ephedrin as a stimulant to the circulation, by its effect on both the heart and the bloodvessels, suggested that its chief therapeutic value might lie in cases of marked circulatory depression, such as occurs in surgical shock, in certain cases of myocardial weakness and in various prolonged low blood pressure conditions. It has been demonstrated how the blood pressure can be temporarily elevated by its use (see Table I) and it was hoped that a continuous blood-pressure increase might result from its administration at fairly frequent intervals over considerable periods of time, but as yet no such effect has been observed. Even in Cases I and II (Addison's disease), in which the patients' general condition seemed to improve while frequent doses were being given, it was found impossible to maintain the pressure constantly at a higher level. It is conceivable, however, that merely frequently repeated temporary elevations may be beneficial aside from any other effects that the drug may have. Case XII would seem to prove this.

CASE XII.—A man, aged sixty-five years, was admitted to the private service of Dr. Alfred Stengel in moderate cardiac decompensation and with marked distention of the urinary bladder from hypertrophy of the prostate. After his bladder had been slowly emptied over a period of several days by Dr. Alexander Randall he developed hiccough, which persisted in spite of all the usual rem-

edies for eight days. At this time his systolic blood-pressure reading was 95 mm. of mercury and his disastolic 55. He was then put on ephedrin in 50-mg. doses by mouth, three times a day, all other medication having been stopped two days before. His systolic pressure promptly rose to 112 to 120 following each injection and the diastolic proportionately. After forty-eight hours the hiccough ceased and during the next two weeks, while still getting the ephedrin, his general condition improved so much that it was considered safe to do the complete radical prostatic operation. This was accomplished under spinal anesthesia by Dr. Randall and the patient is now making an uneventful convalescence and has left the hospital.

There are other cases of a more acute nature, such as those of surgical shock and collapse, in which prompt elevation of the blood pressure for a few hours may be life-saving. Studies of the effect of ephedrin in such cases is being made by Dr. L. K. Ferguson on the neurosurgical service of Dr. Charles H. Frazier and will be reported later. What may be expected in such patients is suggested by the temporary result obtained in the following case:

CASE XIII.—A man, aged forty-two years, who had been operated upon by Dr. E. L. Eliason for an acute intestinal obstruction and who was dying of acute general peritonitis had marked cyanosis and a cold clammy skin with no radial pulse or detectable blood pressure when 100 mg. of ephedrin sulphate were injected into one of his jugular veins. Within ten minutes a systolic blood pressure of 60 mm. of mercury and a diastolic of 50 was obtained, and five minutes later it was 65 systolic and 50 diastolic. He was then given 500 cc of a 10 per cent glucose solution intravenously. At the end of an hour after the first observation the reading was 75 systolic and 40 diastolic. Almost immediately after the ephedrin was injected a radial pulse became palpable and it later grew stronger and fuller during the administration of the sugar solution. After two and a half hours the pressure began to fall (60 systolic and 45 diastolic) and a second dose of ephedrin had no appreciable effect. The patient died ten hours later.

It is believed that other less hopeless cases of this type might be carried through a critical period by such use of ephedrin. Also the cases of sudden heart failure which are often revived by epinephrin might receive a like effect from intravenous or intracardiac administrations of this drug.

The following case of heart block is included because of the very interesting results obtained and the suggestions it may have for those interested in cardiac physiology and therapeutics.

CASE XIV.—A man, aged sixty years, with myocardial disease and generalized arteriosclerosis, fell down stairs and was admitted to the surgical service of Dr. E. L. Eliason with a broken fibula and

complete heart block. His ventricular rate ranged from 34 to 42; his systolic blood pressure was 90 mm. of mercury and his diastolic 50. An electrocardiogram by Dr. Charles C. Wolferth confirmed the cardiac diagnosis. Immediately following this examination the patient was given 100 mg. of ephedrin subcutaneously and subsequent electrocardiograms and blood pressure determinations at ten-minute intervals gave the results tabulated below:

Hour.	Blood pressure.	Electrocardiographic findings.	
		Ventricular rate.	Auricular rate.
11.25 A.M.	90/50	38	110
11.35 A.M.	..	50	125
11.45 A.M.	110/55	Ranged from 55 to 53	125
11.55 A.M.	90/55		125
12.15 P.M.	..		86

On these electrocardiographic studies Dr. Wolferth reported as follows:

"The auricular rate increased from 110 to 125 within ten minutes after injection and remained at 125 for thirty minutes. Fifty minutes after injection the rate had fallen to 86. No disturbances in rhythm were noted. The shape of the *P*-waves changed very markedly.

"The ventricular rate before injection was 38 and occasionally showed slight irregularity. *A–V* dissociation was complete at all times. Ten minutes after injection the ventricular rate had risen to 50 and during the next forty minutes ranged between 50 and 53. The rhythm at this time was regular. Changes were noted from time to time in the shape of the ventricular complexes."

These findings indicate a definite influence of ephedrin on both the ventricles and auricles of the heart when they are acting independently of each other. These effects may be due to stimulation of the cardiac accelerator ganglia or the sympathetic nerve endings, or both, or they may be due to direct action on the heart muscle. These matters will be discussed by Dr. Wolferth and the writer in a subsequent publication when other cases have been studied.

V. **Effects on the Nasal Mucous Membrane.** Among other studies on ephedrin which have been undertaken in this institution is that of the effect of its local application on the nasal mucous membrane by Dr. George Fetterolf and Dr. Marshall B. Sponsler. Their paper is now in the hands of the publishers but they permit me to report that a 5 per cent solution of ephedrin sulphate painted lightly on the mucous surface with a brush caused definite contraction in every one of 17 cases within a few seconds to one minute, the maximal contraction occurring in an average of two and one-third minutes, that the contraction was marked throughout the entire extent of the turbinate even when the drug was applied to only a limited portion of the anterior end and that the lower border was

so contracted as to give the appearance of being drawn upward. The mucosa became so thin and flat that it fit the bones as a glove fits the finger. The color was invariably altered to a paler hue, but there was never the extreme pallor seen with epinephrin. The first evidence of relaxation appeared on an average of two hours and thirty-five minutes after the ephedrin was applied. Finally, and of extreme importance, was the discovery that in none of the cases did there occur any evidence of irritation such as occurs with epinephrin.

This work, therefore, suggests certain distinct advantages of ephedrin over epinephrin in the local treatment of nasal conditions. Its freedom from secondary irritation and the duration of its constricting action suggest that it might also be of value in otolaryngological surgery. Credit for the thought of so using ephedrin locally in the nose belongs to Drs. Alice H. Cook and Otto Willner of Peking, China, who made the suggestion to Dr. Schmidt.

It has been proposed that ephedrin solution might be of equal or even greater value if used as a nasal spray. Such a form of application could be handled by the patient himself and might for that reason be of extreme value in certain local conditions, such as hay fever and acute sinus conditions, which require a more or less continuous effect. This method of applying the drug is now being tried out in our medical wards and will be reported upon at another time.

VI. **Conclusions.** 1. Ephedrin has general physiological effects in man similar to those produced by epinephrin. It has, however, distinct practical advantages over epinephrin because of its more prolonged action and the fact that it can be administered effectively by mouth.

2. In doses of 50 to 125 mg., given orally or subcutaneously, ephedrin sulphate usually raises the systolic and diastolic blood pressure and decreases the pulse rate for a period of several hours. It also stimulates the heart action and has a tendency to increase the output of urine. It sometimes increases the basal metabolism.

3. Its administration caused temporary improvement in 2 cases of Addison's disease, gave relief in the paroxysmal attacks of certain cases of asthma, relieved the subjective sensations in a case of urticaria, caused a disappearance of urticarial lesions in a case of serum disease, and produced marked temporary improvement in a case of circulatory collapse and steady and continuous improvement in a case of circulatory failure incident to myocardial disease and the evacuation of an overfilled urinary bladder.

4. In a single case of complete heart block it produced an increase in both the auricular and the ventricular rates and caused alterations in the character of the electrocardiographic tracings.

5. Locally applied to the nasal mucous membrane, ephedrin causes prompt contraction which persists for more than three hours and has no local irritant effect.

6. It is believed that the widest range of usefulness of ephedrin will be found in the treatment of asthma and of acute circulatory depression, and in the management of certain congestive nasal conditions.

REFERENCES.

1. Nagai: Pharm. Zeit., 1887, **32**, 700.
2. Chen, K. K., and Schmidt, C. F.: Jour. Pharm. and Exp. Ther., 1924, **24**, 339.
3. Miura: Berlin Klin. Wchnschr., 1887, **24**, 707.
4. Amatsu and Kubota: Cited from Chem. Abst., 1918, **12**, 2019.
5. Chen., K. K.: Proc. Soc., Exper. Biol. and Med., 1925, **22**, 404 and 568.
6. Thayer, W. S.: AMER. JOUR. MED. SCI., 1925, **169**, 313.

ONE HUNDRED CONSECUTIVE CHOLECYSTECTOMIES.

A BACTERIOLOGICAL AND HISTOLOGICAL STUDY OF GALL BLADDER LESIONS TOGETHER WITH A HISTOLOGICAL STUDY OF THE ASSOCIATED APPENDICES.

BY WILLIAM O. JOHNSON, M.D.,
CLEVELAND CLINIC, CLEVELAND, OHIO.

THE primary purpose of this study was to determine the relation between histologically pathological gall bladders and the organisms that can be cultured from their fluid contents.

The cases in this group were included among operations performed by five surgeons at the Lakeside Hospital and the Cleveland Clinic Hospital from 1922 to 1924, no selection of the cases being made.

The study was suggested by the belief expressed by many writers, that organisms are always present in the fluid content of all pathological gall bladders. Our purpose, therefore, was not to prove that the isolated organisms produced the lesions in the gall bladder, but merely to determine in what percentage of cases organisms are present in the fluid contents in histologically pathological gall bladders, and the relative frequency of occurrence of different types of organisms.

In none of the cases in which the bacteria were isolated was the fluid content of the gall bladder normal. In nearly all of these there was a definite increase in the amount of mucus, together with a few pus cells and epithelial cells. In 12 instances the gall bladder contained sand without any definite stone formation.

In 3 cases "white bile" was present and in 6 others the gall bladder contained practically no fluid content. In some only a slight amount of mucus with pus cells and a few epithelial cells was obtained, the gall bladders being nearly filled with stones.

In every case the bile was obtained aseptically immediately after removal of the gall bladder and was inoculated within a half hour upon 1 per cent bouillon, blood agar and Endo's medium and incubated at 37° C.

No dilutions of the bile were made in order that the growth obtained might represent, as nearly as possible, the organisms present in a concentration of bile identical with that in the gall bladder.

More positive cultures were obtained from the bouillon media than from any of the other media used. This bears out the study made by Drennan,[1] which showed that bacteria will not grow satisfactorily if more than a 70 per cent concentration of bile is present. The highest percentage of growth was secured from the clearest bile and from that which contained the smallest percentage of bile salts.

The cultures were considered sterile if after a lapse of seventy-two hours no growth was found on any of the media.

For the histological examinations the sections were prepared by fixation in formalin, after which the tissues were mounted in paraffin, being stained after sectioning with eosin and hematoxylin. The histological diagnoses were made by three pathologists. From the available material the following data have been compiled:

The 100 cases studied included 84 females and 16 males. The average age of the females was forty-one years and of the males forty-six years, the youngest being twenty-three years and the oldest seventy-one years of age; 69 of these patients had been married and 57 per cent of the women had borne one or more children; 1 woman had had eleven children.

The average duration of illness prior to the operation, as indicated by the onset of the first definite symptoms, was six and a half years. The shortest duration was three hours and the longest thirty-six years, 1 case having had forty-eight definite attacks prior to operation. Ninety-six patients gave a history of nausea and vomiting. The attacks began at night in 48 cases. Belching or eructation of gas was present in 88 cases. There had been one or more distinct attacks of jaundice in 12 cases; 1 patient had had three attacks before operation, and 3 came to operation with obstructive jaundice. In 71 instances epigastric pain radiating to the back was experienced during the attacks, and in only 46 was there a definite history of pain radiating to the right shoulder—a lower incidence of this symptom than is generally believed. Only 12 patients gave a history of having had typhoid fever. In practically all of the cases there was a history of constipation or costiveness of the bowels. In 8 patients a previous cholecystostomy had been performed.

[1] A Bacteriological Study of the Fluid Contents of One Hundred Gall Bladders Removed at Operation, Ann. Surg., 1922, **76**, 482.

In 9 instances the roentgen-ray films gave positive evidence of stones, and in 6 others a tentative diagnosis of gall bladder disease was made from the roentgenogram.

In practically all of the cases the operation was performed under nitrous oxid-oxygen and local anesthesia with novocain, with the addition of 5 to 25 per cent ether for from two to thirty-five minutes while the exposure and deep dissection were being made. In 22 cases ether was not used. The average duration of anesthesia was sixty-three minutes, the longest period being one hundred and thirty-six minutes.

The primary incision was right rectus in 86 cases, pararectus in 10 and transverse epigastric in 4 cases.

In 58 instances the gall bladder was dissected from the cystic duct toward the fundus of the gall bladder, the cystic duct and artery being separately ligated in every case. In 86 of the cases the cystic duct was doubly ligated, proximal to the common duct with catgut, and distal to this ligature with silk.

In practically all of the cases in which there were adhesions the adhesions were dissected free and the gall bladder was dissected from the fundus toward the cystic duct. In 15 cases the serosa was sutured over the gall bladder bed to check oozing.

In 99 instances drainage was obtained by from one to three cigarette drains. In 2 cases there was drainage of bile which in 1 persisted for sixteen days and caused a necrotic slough of the subcutaneous tissue in the right hypochondrium. In 8 cases drainage was established through the flank by the insertion of cigarette drains through a stab wound below the costal margin. The drains were removed in from six to eight days.

Two cases were complicated by the presence of stones in the common duct, the typhoid bacillus being isolated in 1 of these. In 3 patients the gall bladder contained "white bile," and in 2 of these stones were impacted in the cystic duct.

The operative notes in 13 instances mention enlargement of the periductal glands and scarring and cirrhotic changes in the liver in the gall bladder region. In 4 cases it is stated that the pancreas was enlarged and hard.

The hospital period varied from three to forty-seven days, the average period being eighteen and a half days.

The operative mortality in this series was 3 per cent, the causes of death being respectively pneumonia, acute dilatation of the heart with acute edema of the lungs, and acute nephritis superimposed upon a chronic nephritis. In 3 cases there was an acute suppression of urine, which in 2 cleared up after the second day.

The gross description of the gall bladder specimens mentions adhesions on the gall bladder wall in 41 cases; a definite increase of the fat deposit in the gall bladder wall in 28; thick, tenacious, dark green bile containing a large amount of mucus in 47, and thick gall bladder walls in 31.

The stones varied greatly in size, shape and consistency, being described as soft crumbly sand in 11 cases; in 1 instance seventy-eight stones were present.

TABLE I.

Patient.	No.	Average age in years.	Average duration symptoms, years.	Infected fluids.	Sterile fluids.	Cholecystitis with stones.	Cholecystitis without stones.
Women . .	84	41	8½	24	60	52	32
Men . .	16	46	4	8	8	10	6

The bacteriological study of the fluid contents of these gall bladders showed positive cultures in 32, these being pure cultures of B. coli in 18, staphylococcus and B. coli in 2 cases and streptococcus or staphylococcus or both in 11; in 1 patient the B. typhosus was isolated. (See Table II.)

TABLE II.—DIAGNOSIS ASSOCIATED WITH DIFFERENT TYPES OF GALL-BLADDER LESIONS AS DETERMINED IN A STUDY OF ONE HUNDRED CASES.*

Type of lesion as histologically determined.	Bacillus coli.	Staphylococcus aureus.	Streptococcus.	Staphylococcus albus.	Typhoid bacillus.	Bacillus coli and staphylococcus.	Streptococcus and staphylococcus.	Sterile.	Total.
Acute cholecystitis without stones . .	2	..	..	..	..	1	..	1	4
Acute cholecystitis with stones . . .	1	..	..	..	..	..	..	..	1
Acute and chronic cholecystitis with stones	2	1	..	..	..	..	..	5	8
Chronic fibrous cholecystitis without stones	3	1	..	..	..	1	..	30	35
Chronic fibrous cholecystitis with stones	7	3	..	1	..	..	..	27	38
Subacute cholecystitis with stones . .	..	2	..	..	..	..	1	..	3
Subacute and chronic cholecystitis . .	..	..	..	..	..	..	..	3	3
Empyema of gall bladder	..	..	..	..	..	..	1	..	1
Hydrops of gall bladder	..	..	1	..	..	..	..	..	1
Subacute and pericholecystitis . . .	2	..	..	..	1	..	..	1	4
Normal gall bladder	1	..	..	..	..	..	..	1	2
Total	18	7	1	1	1	2	2	68	100

* The diagnosis as stated is based on the histological findings, the presence of stones being added to the histological findings in the cases in which they were present.

In 52 of these patients an appendectomy was performed together with the cholecystectomy. The histological diagnosis in each of

these has been tabulated together with that of the associated gall bladder. (Table III.)

TABLE III.—TYPES OF LESIONS OF THE APPENDIX ASSOCIATED WITH VARIOUS TYPES OF GALL BLADDER LESIONS IN FIFTY-TWO CASES.*

	Chronic fibrous appendicitis.	Obliterative appendicitis.	Peri-appendicitis.	Acute appendicitis.	Subacute appendicitis.	Normal appendix.	Total.
Acute cholecystitis without stones							
Acute cholecystitis with stones							
Acute and chronic cholecystitis with stones	1	1	..	..	..	..	2
Chronic fibrous cholecystitis without stones	10	9	2	..	1	2	24
Chronic fibrous cholecystitis with stones	5	7	1	..	..	4	17
Subacute cholecystitis with stones	1	1	..	..	..	..	2
Subacute and chronic cholecystitis (gastrectomy tube)	1	..	..	..	..	1	2
Empyema of gall bladder	..	..	..	1	..	..	1
Hydrops of gall bladder	..	..	..	..	1	..	1
Subacute and pericholecystitis	..	..	..	..	1	..	1
Normal gall bladder	1	..	..	..	1	..	2
Stone in cystic duct							
Total	19	18	3	1	4	7	52

* The type of lesion of both the gall bladder and the appendix was determined in each case by histological examination.

Conclusion. 1. Organisms were cultured from the fluid contents of pathological gall bladders in less than one-third of the cases in this series.

2. B. coli was the predominating organism in the positive cultures.

3. The highest percentage of positive cultures was obtained from the gall bladders which contained the lowest percentage of bile salts.

4. Even after double ligation of the cystic duct there was an escape of bile in 2 cases, a finding which reinforces the argument for drainage of the abdomen after cholecystectomy.

5. Histological changes seem to indicate that the lesions in the appendix are of longer duration than the other associated gall bladder lesions.

6. Histologically pathological gall bladders with culturable organisms in their fluid content have a far higher mucus content than normal gall bladders. The walls show an increase in fat content and thickening.

A REVIEW OF TWENTY-EIGHT CASES OF PURPURA HEMORRHAGICA IN WHICH SPLENECTOMY WAS PERFORMED.*

By Herbert Z. Giffin, M.D.,
DIVISION OF MEDICINE, MAYO CLINIC,
AND
Jackson K. Holloway, M.D.,
FELLOW IN SURGERY, THE MAYO FOUNDATION, ROCHESTER, MINN.

The recommendation of splenectomy in the treatment of cases of hemorrhagic purpura is based on the apparent importance of the reduced number of platelets and their morphologic abnormality, together with the accumulated data which showed an increase in the number of platelets following splenectomy in experimental animals and also in man when operation has been performed for other conditions. The good temporary effect of radiation of the spleen in hemorrhagic diseases in general is a contributing consideration.

This paper, which has been prepared in the hope that it may be valuable for reference, consists of a review of 28 cases in which splenectomy has been performed for purpura hemorrhagica. Nineteen of the cases have been reported in the literature, 8 have been previously reported from the Mayo Clinic, and 1 other case from the Clinic has not been previously reported. Short abstracts of all of the cases, and a summary of the various features are presented.

Abstract of Cases. Case I.—Kaznelson's first case was that of a woman, aged thirty-six years, who had had petechiæ and purpuric areas since childhood. In the preceding ten years she had had three severe attacks of hemorrhagic purpura, the erythrocytes on one occasion dropping to 940,000. During a remission in 1910 the patient had given birth to a child, apparently without incident. At the time of splenectomy the erythrocytes numbered 3,100,000, the leukocytes 2760 and the platelets 600, many of which were of the giant form. A few myelocytes and normoblasts were present in the smears. The spleen was palpable.

Splenectomy was performed in 1916. A few days after operation the platelets had risen to 600,000, clot was retractible, and the bleeding time normal. In fourteen days purpura and petechiæ had disappeared. The menstrual period decreased in duration from ten to three days. Later the platelet count dropped from 600,000 to 100,000, and irregular forms of platelets were again to be seen. However, clot retraction was normal and hemorrhage did not recur. In three months the anemia had disappeared. The patient was reported in excellent health and free from hemorrhage five years later.

* Submitted for publication, May 4, 1925.

CASE II.—In 1917 Benecke reported a splenectomy on an unmarried woman, aged twenty-one years. Three years previously the patient had been under observation with anemia, epistaxis, and a pelvic condition which was probably due to hemorrhage although extra-uterine pregnancy had been suspected. At that time the hemoglobin was 35 per cent. Four months previous to the operation the patient was readmitted on account of severe anemia and prolonged menstruation. Apparently she had had petechiæ and purpura, together with epistaxis and prolonged menstruation, since the preceding examination. The hemoglobin was 30 per cent, the erythrocytes numbered 2,100,000, the leukocytes 3200 and the platelets 47,891. Medical measures failed to improve the anemia. Three months preceding the operation the hemoglobin was 30 per cent, and the platelets 38,370, and ten days preceding the operation the erythrocytes numbered 2,150,000, and the platelets 66,053. The spleen was not palpable.

Splenectomy was performed July 13, 1917. The spleen weighed 250 gm. and there was hyperplasia of the malpighian corpuscles. A smear from the spleen showed many platelets. On the third day after operation the erythrocytes numbered 3,250,000, the leukocytes 11,030, and the platelets 344,076. Two weeks after operation the hemoglobin was 42 per cent, the erythrocytes 3,580,000, the leukocytes 7400 and the platelets 664,000. A normal menstruation occurred. The patient was dismissed in a very satisfactory condition two months after operation; the hemoglobin was then 52 per cent, erythrocytes 4,176,000 leukocytes 4900, and platelets 577,800. Three months after operation the patient was apparently well.

CASE III.—Kaznelson's second case was reported in 1919. The patient was an unmarried woman, aged twenty-five years, who had suffered from purpura, epistaxis, and menorrhagia for five years, especially during the summer months. Preceding operation the platelet count was 500, the clot was non-retractile. During an acute exacerbation the erythrocytes fell very rapidly from 5,000,000 to less than 1,000,000. The spleen was barely palpable.

Splenectomy was performed November 18, 1916. Two hours afterward the platelet count had risen to 408,000 and the clot was retractile. The platelet curve decreased later to 20,000; however, the clot was still retractile, and slight epistaxis occurred but no serious bleeding either then or subsequently. Five months after the operation the platelet count was 33,000, and at one time had been as low as 10,000. There had been slight epistaxis at times, but no other bleeding. The menstruation lasted for three or four days, whereas formerly it had lasted ten days or more. Five years after splenectomy the patient had had no recurrence of hemorrhage and was apparently well.

CASE IV.—Kaznelson's third case was also reported in 1919. The patient was a girl, aged eleven years, who had had petechiæ, purpura, epistaxis, and hemorrhagic crises for three years. The platelet count was 6700; the clot non-retractile. The spleen was not palpable.

Splenectomy was performed December 18, 1916. Three days after splenectomy the platelet count was 267,000; in seven days it had dropped to 13,000 and moderate epistaxis and hematemesis occurred. The platelet count subsequently varied from 5000 to 28,000, and the patient continued to have a few petechiæ, but no ecchymosis, and epistaxis only rarely. Five years later the patient was also reported to be well without recurrence.

CASE V.—Minkowski, in 1919, reported a splenectomy performed on a man, aged fifty-three years. The patient had had petechiæ and purpura for several years, and epistaxis for two and a half years. Platelet counts varied from 14,000 to 29,000. The coagulation time varied from eight to fifteen minutes, the bleeding time was nineteen minutes; the tourniquet test was positive. Hemoglobin was 56 per cent, the erythrocytes numbered 5,200,000 and leukocytes 5400. The spleen was not palpable.

Splenectomy was performed October 7, 1919. The spleen, pathologically, was not large and showed no striking changes. Many platelets were present in smears. Seven hours after splenectomy the platelet count was 56,000; two days after splenectomy it was 100,000; and twenty-three days after it was 60,000. Twenty-one days after operation epistaxis occurred, and the bleeding time was found to be prolonged to fifteen minutes. One month after operation the platelet count was 25,000. Two months after operation there had been no further bleeding and the bleeding time was seven minutes.

CASE VI.—Ehrenberg, in 1920, reported a splenectomy on a girl, aged nineteen years, who formerly had had petechiæ for ten days preceding and during each menstruation. Menstruation was very profuse. Blood platelets were practically absent and the bleeding time was prolonged, especially preceding menstruation. It was usually between thirteen and twenty minutes, once it was ninety-seven minutes and once it was two hours. The coagulation time was usually normal. The spleen was not palpable.

Splenectomy was performed in 1918. Two and a half hours after splenectomy the platelet count had risen to 87,500. The following day it was 118,425, and five days afterward it was 684,700. The platelet count then gradually became reduced to 13,000 and later to 4000. The bleeding time varied from three minutes to six minutes; the anemia and purpura disappeared, and the menstruation became normal.

CASE VII.—Kaznelson, in 1921, reported a case of hemorrhagic purpura. The patient died at operation, apparently a "heart death." Details are not given.

CASE VIII.—Kaznelson reported his fifth case also in 1921, that of a woman, age not given, in whom splenectomy was successful. The platelets rose from 38,000 to 550,000. A protocol was not published.

CASE IX.—Minot, in 1921, reported a case in which splenectomy was performed in September, 1920, with favorable result. Details are not given. This patient was reported to be in good health two and a half years later. The platelet count before operation was 10,000, and after operation 300,000.

CASE X.—Retzlaff, in May, 1921, successfully performed a splenectomy for purpura hemorrhagica. Details are not given.

CASE XI.—Cori, in 1922, reported a splenectomy performed on a girl, aged thirteen years. She had had petechiæ, purpura and occasional epistaxis for four years, and once suffered prolonged bleeding after the extraction of a tooth. The father and the father's brother had had frequent epistaxis. The platelet count was extremely low, the bleeding time was six minutes, and the clot showed no retraction. The leukocytes numbered 8800, the erythrocytes 2,000,000. Normoblasts and myelocytes were present. The spleen was palpable.

Splenectomy was performed February 24, 1921. The spleen weighed 120 gm. Following the operation the platelet counts were 109,000 five hours after operation; 386,000 on the third day; 740,000 on the eighth day; 741,000 on the fifteenth day; 271,000 three months after operation; 280,000 four months after operation, and 145,000 eight months after operation. Five hours after operation the bleeding time was three minutes and the clot was retractile. Menstruation which had not occurred previously was established normally in seven months. Within ten months the platelet count had become reduced to 23,000, but bleeding had not recurred.

CASE XII.—Cori, in 1922, reported a second case. The patient was a woman, aged twenty-one years, who had suffered from profuse menorrhagia and had bled excessively after the extraction of a tooth. The platelet count before operation was very low. The spleen was palpable.

Splenectomy was performed November 27, 1921. The spleen weighed 320 gm., and contained many platelets. Eight hours after operation the platelet count was 63,750; the next day it was 307,000; on the fourth day it was 820,000; on the sixth day 862,000;

on the eighteenth day 1,150,000, and on the nineteenth day 89,500. Malarial parasites were found in the blood and the patient died from subphrenic abscess one month after splenectomy.

CASE XIII.—Steinbrinck, in 1922, reported the case of a girl, aged five years. At the age of two and a half years, she began to have crops of petechiæ and thrombopenia. Platelet counts ranged from 1300 to 18,000. Ten months later there was a recurrence. Two years later she had nose bleeds, and vomited blood. The spleen was not then palpable. Bleeding time was twelve minutes, and retraction of clot was incomplete after twelve hours. The platelet count was 700. As a result of continuous bleeding the hemoglobin was reduced to 15 per cent, and the erythrocytes to 1,770,000; the leukocytes numbered 12,100. The spleen was palpable at times.

Splenectomy was performed September 3, 1921. Bleeding ceased promptly. The platelets apparently did not increase, the count varying from 8000 to 18,000; many of the platelets were large and deformed. A splenic extract contained very few platelets. Nine weeks after operation the patient was in good general condition; there was no bleeding or petechial eruption. The tourniquet test however, was positive and the bleeding time was forty-one minutes. The leukocyte counts varied from 4330 to 26,400. Later the bleeding time was five and a half minutes and the clot showed feeble retraction after twenty-four hours. Five months after operation there was slight epistaxis and a few petechiæ, but the patient's general condition was good.

CASE XIV.—Bowen, in 1923, reported the case of a man, aged twenty-two years, who had had symptoms of purpura for eighteen years. Three months preceding operation there had been severe epistaxis, melena and bleeding from the gums. The hemoglobin was 18 per cent; erythrocytes numbered 1,648,000; the leukocytes 4800, of which 75 per cent were polymorphonuclears. The number of blood platelets was much decreased and the bleeding time varied from twenty minutes to two hours. The clot was non-retractile. Transfusions were given, and four days before operation the erythrocytes numbered 5,000,000, but the platelet count remained low, 2500. The spleen was palpable.

Splenectomy was performed August 28, 1922. Two hours after operation the platelet count was 17,000; within four hours it was 22,000; and the next day it was 190,000. The bleeding time was reduced to four minutes. Nine days after operation the platelet count was 608,000, and three weeks after operation it was 307,000. The patient was apparently in good condition. However, at the end of the fourth week he developed jaundice probably of the catarrhal type, and the platelet count became reduced to 100,000. One

month after operation the platelet count was 57,000, and the bleeding time was prolonged to fourteen minutes. In the ninth week the platelet count was 20,000, the bleeding time was seventy minutes, and slight epistaxis and purpura occurred. Twelve weeks after operation the jaundice began to clear; the platelet count was 50,000, the bleeding time twelve minutes. Four months after operation there had been no recurrence of bleeding; the platelet count was 95,000, and the bleeding-time eight minutes.

CASE XV.—Brill and Rosenthal in 1923, presented the first case in which splenectomy was performed, and which attracted general attention in this country. The patient, a girl, aged nineteen years, had had severe epistaxis at least once a year since the age of five. Purpura occurred and later prolonged menstruation. Eight transfusions had been given in the preceding eight years without permanent benefit. She was admitted to the Mt. Sinai Hospital, October 26, 1922, after three days of hematemesis and severe bleeding from the gums and nose. The hemoglobin was 38 per cent, the erythrocytes numbered 2,272,000, the leukocytes 6800, and the platelets 6400. The coagulation time was ten minutes (Lee); the bleeding-time ten plus minutes. The tourniquet test was positive. Clot retraction was absent. Direct transfusions of blood, and horse serum were given. The spleen was easily palpable.

Splenectomy was performed December 2, 1922. The spleen weighed 1400 gm. Microscopically it showed "myeloid metaplasia and hypertrophy of the malpighian bodies;" blood platelets were not seen. A fresh crop of petechiæ appeared and there was slight bleeding from the gums a few hours after operation, but later bleeding ceased. After operation the leukocytes increased to 56,000, later fluctuating between 8000 and 28,000. The platelets numbered 95,000 six hours after operation; one day later 225,000; and a week later 5000. The bleeding time was usually normal but occasionally prolonged. The tourniquet test was usually negative. Clot retractility was present the first month, absent the second month and present again the third month.

CASE XVI.—Brill and Rosenthal's second case was that of a boy, aged fifteen years. His illness began in April, 1919, with tonsillitis followed by petechiæ, bleeding from the gums, and painful joints with which he was confined to the hospital a month. Following this illness he had severe nose bleed in May, 1922, and occasional purpura on injury. Epistaxis recurred in July and November, 1922. He was admitted to the hospital November 22, 1922. A petechial eruption and bleeding from the gums were present. The patient was very anemic; the tourniquet test was at times positive, and at times negative; clot retraction was absent; the bleeding time was slightly prolonged, and at times normal. The leukocyte count was 10,000. The spleen was not palpable.

Splenectomy was performed December 30, 1922. The spleen was soft and slightly enlarged, weighing 300 gm. The malpighian bodies were visible. Oozing from the nose and wound stopped immediately after removal of the spleen, and the bleeding time was reduced to three minutes. Clot retraction was first present six weeks later. For a month following operation occasional crops of petechiæ and slight nose bleed occurred. One day after operation the platelet count was 31,200. The third day it fell to 1000, then gradually rose to 10,000 and 20,000. The bleeding time was slightly prolonged for a month.

CASE XVII.—Wild, in 1923, reported the case of a boy, aged fifteen years. A family history of bleeding had not been obtained. The patient had been subject to bleeding since early childhood, including bleeding from wounds, and extraction of a tooth had been followed by severe bleeding. At the age of eight, he had a hematoma at the knee, and anemia, at which time a diagnosis of hemophilia was made. On the morning of admission June 7, 1922, he experienced a sudden severe pain in the left side of the abdomen while straining at stool. He grew pale and was taken to the hospital. Ecchymoses but no petechiæ were found on various parts of the body. The hemoglobin was 36 per cent; the erythrocytes numbered 2,400,000. A diagnosis of rupture of the spleen was made, and a transfusion was given.

Splenectomy June 7, 1922 disclosed a rupture 5 cm. in length in a spleen which weighed 340 gm. The abdomen contained a large quantity of blood. Transfusion was necessary following operation. The day of the operation, the platelets numbered 92,500; the bleeding time was five minutes. On the following day the platelets numbered 81,000; the bleeding time was six and a half minutes. Five days after operation, the platelets numbered 324,000; on the thirteenth day 1,033,000; five weeks after operation 820,000; the bleeding time was two minutes. Nine months after operation the general health was excellent and there had been no recurrence of purpura. The coagulation time was persistently twenty minutes or longer, which is suggestive of a mild hemophilia.

CASE XVIII.—Hitzrot, in 1923, reported the case of a girl, aged eight years, who had had symptoms of purpura with epistaxis for three years. One month before operation there was an acute exacerbation accompanied by melena and hematemesis. The hemoglobin was 40 per cent, the erythrocytes numbered 2,400,000, the leukocytes 38,000 and platelets 40,500. The bleeding time was longer than twenty minutes, and the clot was non-retractile. The spleen was palpable.

Splenectomy was performed February 27, 1923. After the operation the platelet count rose to 600,000 and the bleeding time became

reduced to five minutes. Two months later the platelets were abundant and the bleeding time was two and a half minutes. Three months after operation there was continued general improvement and bleeding had not recurred.

The spleen in this case weighed 120 gm. (the patient's weight was only 47.5 pounds). On microscopic examination the lymphoid follicles showed large socalled germinal centers. Polymorphonuclear leukocytes and myelocytes were present in moderately large numbers, and the eosinophils were increased in number; collections of blood platelets were not seen.

CASE XIX.—Cohn and Lemann reported the case of a boy, aged five and a half years, who was first seen February 25, 1923. A history of familial bleeding was not obtained. Purpuric areas from 1 to 2.5 cm. had appeared recently. The tonsils had been removed several weeks previously. Slight anemia was present and the blood smears contained but few platelets. There was a recurrence of the purpura which did not subside after transfusion. The spleen was not palpable.

Splenectomy was performed June 3, 1923; the spleen was slightly enlarged. Shortly after operation there was a peculiar reaction, anaphylactic in type. This was thought to be due possibly to the expression of a toxic material from the spleen at operation. Following pneumonia recovery was satisfactory. Seven weeks after operation the platelet count was 145,000; four months after operation it was 200,000. Within six months the general condition was satisfactory and there had been no recurrence of purpura.

The remaining cases were observed at the Mayo Clinic. Eight of them have been reported in more detail elsewhere.

CASE XX.—A woman, aged thirty-one years, came under observation December 20, 1922. In October, 1921, petechiæ and ecchymoses had been noted and were more or less continuous afterward. In December, a tooth had been extracted with excessive bleeding. On October 1, 1922, severe epistaxis occurred and recurred, transfusions finally becoming necessary. November 3, uterine bleeding began and became excessive; transfusions again became necessary. There was no bleeding from bladder or gastrointestinal tract. Platelet counts were consistently below 100,000, and not infrequently below 50,000. The bleeding time was prolonged; the clot was nonretractile. During two months of personal observation, twelve transfusions were given. The hemoglobin dropped at one time to 18 per cent; the erythrocytes to 1,610,000. The spleen was palpable.

Splenectomy was performed March 7, 1923. The spleen was somewhat enlarged and weighed 210 gm. Six hours after operation the platelets numbered 202,000 and the bleeding-time was normal. The platelets numbered 727,000 on the eighth day and on the six-

teenth day 365,000. Slight uterine oozing occurred the third and fourth days, but did not recur. All evidence of purpura disappeared. Two years later the patient was still in good health.

CASE XXI.—A girl, aged twenty-three years, was admitted to the clinic June 12, 1923 on account of excessive menstruation. She had had ecchymoses on slight injury for thirteen years. Five years previously menstruation became very excessive and she was confined to bed for five months. Nose bleeds had been frequent between the ages of fifteen and nineteen. At the time of admission she was moderately anemic; the platelets varying from 28,000 to 100,000, the bleeding time was prolonged. Transfusions were given with temporary benefit, but excessive menstruation and other manifestations of purpura continued. The spleen was palpable.

Splenectomy was performed October 29, 1923. The spleen weighed 200 gm. The following day the platelets numbered 146,000, on the sixth day 638,000. All signs of purpura promptly disappeared and menstruation became normal. One year later after a severe reaction following vaccination a crop of petechiæ appeared but faded in a few days. The menstruation did not become excessive. Seventeen months after operation the patient is apparently well.

CASE XXII.—A man, aged twenty-four years, was first seen January 9, 1920. For twelve years he had had severe nose bleeds. Slight oozing from the gums was almost continuous, and petechiæ appeared frequently. Moderately severe anemia was present chiefly as a result of epistaxis. One Wassermann test was positive but an investigation for syphilis was negative. Improvement followed transfusion. The patient returned at intervals; he did not have severe hemorrhages, but he could not exert himself because of the development of petechiæ, ecchymoses and bleeding from the gums. Uusually the platelets were under 100,000. The tourniquet test was positive; the clot was non-retractile. Bleeding time was occasionally prolonged. The spleen was not palpable.

Splenectomy was performed February 22, 1924. The spleen weighed 220 gm. Bleeding from the gums ceased immediately. Slight nose bleed recurred on the fifth day, but after that time all manifestations of purpura disappeared. Two weeks after operation the platelets numbered 260,000; the bleeding time was two minutes. Thirteen months after operation the patient apparently is well.

CASE XXIII.—A girl, aged eleven years, was admitted March 11, 1924, because of epistaxis, petechiæ and ecchymoses, which had been recurrent for five and a half years. Three years previously she had been confined to the hospital seven weeks and was transfused. The patient was moderately anemic; the platelets numbered

less than 50,000; the bleeding time varied from thirty-eight minutes to one hour. A tourniquet test was positive. The spleen was easily palpable.

Splenectomy was performed March 18, 1924. The spleen weighed 168 gm. (the child weighed 92 pounds). By the fifth day the platelet count had risen to 430,000, and the bleeding time had become reduced to two and a half minutes. The patient had nose bleed the second day after operation. From four to six weeks after operation the patient suffered from a severe cold, and had slight nose bleed and a few petechiæ. One year following splenectomy there has been no recurrence of purpuric manifestations and the patient is in excellent health.

CASE XXIV.—A man, aged thirty-two years, came under observation August 28, 1924. Two years previously he began to have purpuric areas on the slightest injury which would spread widely before beginning to clear up. Petechiæ occurred and scratches would bleed excessively. He had bleeding from scratches on the scalp, bleeding into the sclerotics, and bleeding from nose and gums. Blood was passed in the urine and stools. At times purpuric areas would leave nodules under the skin, and a mild degree of arthritic pain was complained of. The platelet count was 36,000, the bleeding time was fifteen minutes; the tourniquet test was positive; and the clot was non-retractile in two hours. The spleen was barely palpable.

Splenectomy was performed October 8, 1924. The spleen weighed 164 gm. On the sixth day the platelets numbered 684,000, and the bleeding time was five minutes. On the eleventh day the platelets numbered 816,000; the bleeding time was two and a half minutes. The massive purpuric areas and other manifestations of purpura never recurred, and the arthritic pains disappeared. The patient continues to be in good health five months after operation.

CASE XXV.—A girl, aged eleven years, was admitted September 22, 1924. Petechiæ had appeared suddenly five and a half years before, since which time petechiæ had recurred with ecchymoses and epistaxis. The gums bled easily, and there had been occasional bleeding into the sclerotics. Bleeding from the vagina once followed a fall, and bleeding from the bowel had been noted. At the time of admission the slightest exertion brought on bleeding and at times attacks of fever to 101° F. Marked anemia was present. The platelets numbered 54,000; the bleeding time was ten minutes; the tourniquet test was positive; and retractility of the clot did not occur in three hours. On two occasions the platelets rose temporarily to 180,000. The spleen was easily palpable and firm.

Splenectomy was performed October 10, 1924. The spleen weighed 202 gm. and was definitely enlarged in comparison with the

weight of the patient. On the third day the platelets numbered 643,000, and the bleeding time was three and a half minutes. The highest platelet count was 780,000 on the sixth day. Eighteen days after operation the platelet count became reduced to 88,000 but the bleeding time was two and a half minutes. No fresh hemorrhages occurred. Five months after operation the patient continued in good health.

CASE XXVI.—A girl, aged fifteen years, was examined September 24, 1924. Petechiæ and purpura had been present for ten years. Epistaxis had occasionally occurred. Bleeding from the gums had never been troublesome. Menstruation began at thirteen, occurred at intervals of from four to six weeks, and lasted from four to thirty days. At the onset of menstruation she had been confined to the hospital for five weeks and was given several transfusions. At the time of admission the hemoglobin was 14 per cent, the erythrocytes numbered 1,370,000, and the platelets 42,000. The bleeding time was six minutes; clot retractility was absent in twenty-four hours. Following one transfusion improvement was very rapid. The platelets varied from 42,000 to 166,000, but most of the time were in the neighborhood of 100,000. The spleen was palpable and firm.

Splenectomy was performed October 16, 1924. The spleen weighed only 125 gm. but at the time of operation was estimated as twice normal size. No bleeding occurred after operation. The platelets on the third day numbered only 64,000, on the fifth day 516,000, but the bleeding time was prolonged, seven and a half minutes, and retractility of clot did not occur in six hours. Even on dismissal, the fifteenth day, the bleeding time was six and a half minutes. Clot retraction was not satisfactory in twenty-four hours, although the platelets numbered 408,000. Symptoms had not recurred five months later.

CASE XXVII.—A girl, aged eighteen years, was admitted January 30, 1920. Menstruation had begun five years previously with profuse bleeding, necessitating absolute rest for four weeks and uterine packs. More or less frequent periods of disability occurred because of uterine hemorrhages. Nose bleeds had occurred since childhood, ecchymoses and petechiæ had been present for at least five years, and bleeding from the gums had been continuous for a year. The hemoglobin was 15 per cent; the erythrocytes numbered 1,800,000. After a series of four transfusions the blood was normal.

Curettage was performed April 24, after which no serious difficulty with uterine hemorrhage was experienced. The patient was under observation for four years and was at all times partially disabled by petechiæ, ecchymoses, bleeding from the gums, and occasionally profuse menstruation. The platelets varied from 42,000 to 72,000 with occasional elevations above 100,000, and once

it was 206,000. The bleeding time was prolonged; the tourniquet test was positive; the clot was non-retractile. The spleen was not palpable.

Splenectomy was performed October 23, 1924. The spleen weighed, after loss of its blood, only 92 gm. Four hours after operation the platelets numbered 200,000; on the ninth day 840,000. On the fifth day there was slight retraction of the clot in thirty minutes. All hemorrhagic manifestations ceased. Five months later the patient was in excellent health.

The following case has not been previously reported, and the data will therefore be given more in detail. It constitutes the ninth case of our series.

CASE XXVIII.—A man, aged twenty-seven years, came under observation February 19, 1924. There was no history of hemophilia, purpura, or epistaxis in the family. He had had severe recurrent hemorrhages from the nose for a period of eight months. For six months large and small purpuric areas had appeared on the body, especially on the arms and legs. Bleeding from the gums had occurred at times, and on several occasions hemorrhages into the conjunctiva.

Petechiæ were present. The hemoglobin was 73 per cent, the erythrocytes numbered 4,480,000, and leukocytes 13,200; the differential count was not abnormal. The platelets varied from 52,000 to 134,000; the bleeding time was from three to twenty minutes; the coagulation time by the Boggs method varied from four and a half to nine minutes, and by the Lee method it was twelve minutes; the calcium time was twelve minutes; the prothrombin time was not definitely prolonged. A tourniquet test was positive. The clot did not retract satisfactorily in twenty-four hours. Large septic tonsils, an area of periapical infection and a traumatic ulcer on the septum were noted. Three injections of 20 cc of whole blood subcutaneously were given. These were followed by extraction of one tooth March 6, and by tonsillectomy March 11. Following tonsillectomy, oozing continued at intervals for six days and the patient became pale. The erythrocytes dropped to 2,990,000, and the hemoglobin was 45 per cent. Two transfusions were then given; bleeding ceased after the first one.

The patient was dismissed March 28, 1924, and returned September 24. There had been no serious hemorrhage since the former dismissal, although bleeding from the gums and purpuric areas recurred. The blood platelets were 102,000, coagulation time by the Boggs method was five and a half minutes and bleeding time three minutes; coagulation time by the Lee method was thirteen minutes, calcium time was twelve minutes, and the prothrombin time was slightly prolonged. The tourniquet test was not definitely positive.

The patient was dismissed September 25, 1924, and returned January 12, 1925. Epistaxis had occurred three times, and there was bleeding from the gums on the slightest trauma. The tourniquet test was positive. The blood count was normal, the platelets numbered 50,000, the coagulation time by the Boggs method eight and a half minutes, bleeding time four minutes, coagulation time by the Lee method nine and a half minutes, and calcium time fifteen minutes. The prothrombin time was definitely prolonged. Clot retraction was absent at two hours and very slight at four hours. The erythrocytes showed normal fragility. The spleen had not been palpable at any time while this patient was under observation.

Splenectomy was performed January 12. The spleen was described as being slightly larger than normal, but it weighed only 140 gm. The patient's convalescence was satisfactory. On the eighth day after operation the blood platelets numbered 360,000; on the thirteenth day they had risen to 504,000. The bleeding time was normal after operation. On the eleventh day the coagulation time by the Lee method was six minutes, the calcium time was eight and a half minutes. Three weeks after operation the hemoglobin was 67 per cent, erythrocytes numbered 3,840,000, and the leukocytes 10,600. The differential count showed nothing of special importance. The platelets numbered 308,000; the coagulation time by the Boggs method was six minutes, by the Lee method nine minutes, the bleeding time was two minutes, the calcium time ten and a half minutes, and prothrombin time normal. Retractility of the clot was slight in one hour, marked in two hours, and apparently complete in five hours. The tourniquet test was negative. Three months after operation the patient was well.

Summary. *The Clinical History.* Most of the histories in the collected series of cases exemplify the chronic recurrent type of purpura hemorrhagica with low platelet count, non-retractile clot, long bleeding time, and positive tourniquet or capillary resistance test. In many cases petechiæ and ecchymoses dated from childhood. Bleeding in most cases was from the nose, gums, and uterus. Bleeding from the bowel occurred in 4 cases and from the bladder in 1. In 3 blood was vomited. Extraction of teeth and tonsillectomy were quite frequently followed by troublesome oozing even after preliminary preparation. Bleeding into the sclerotics was noted in 2 cases. The patient in Case I during a remission had given birth to a child without serious incident; in Case II, in which extrauterine pregnancy had been suspected, the pelvic condition was probably due to hemorrhage. In Case XXIV purpuric areas became quite extensive before beginning to clear up, and some of these developed into subcutaneous hematomas leaving nodules which disappeared very slowly; troublesome bleeding occurred from scratches.

In Case XI the patient's father and father's brother had had frequent epistaxis, but the patient did not have hemophilia. In Case XVIII the purpura had existed since infancy and a hematoma occurred at the knee when the boy was eight. He was admitted with a rupture of the spleen following straining at stool. Splenectomy was performed with a subsequent disappearance of all hemorrhagic manifestations. The platelets were said to be few in number on inspection of the smears before operation, but the coagulation features had some of the characteristics of hemophilia. The author, however, believed that hemophilia had been excluded. In Case XXVII curettage was effective in arresting severe metrorrhagia; the menstruation was somewhat profuse but not excessively so afterward up to the time of splenectomy four and a half years later. This observation may be important in the control of uterine hemorrhage which frequently persists in spite of packing and the use of coagulants and transfusions; the result of curettage is usually feared in such cases, possibly unnecessarily in view of the fact that in cases of purpura hemorrhagica gross wounds do not cause uncontrollable bleeding. Patients are known to have had major operations in the course of the disease aside from removal of the spleen.

The use of coagulants was ineffectual or only temporarily effectual. Subcutaneous injection of whole blood seemed to be more effective than coagulants. Radium exposures over the spleen were also temporarily effective. In the Mayo Clinic series, transfusions by the citrate method were efficacious in improving the patient's general condition and the blood, and in most instances in decreasing the amount of bleeding and preparing them for splenectomy. Absolute rest in bed and quietness in bed are essentials in the medical care.

In Cases XVI and XXIV arthritic pain was a prominent complaint but actual arthritis and hemorrhage into the joint were not demonstrated. This symptom disappeared promptly after splenectomy.

In Case XXII a Wassermann reaction was positive but a thorough investigation for syphilis was negative. It is no longer surprising to obtain a false positive Wassermann reaction in any serious blood dyscrasia.

The duration of the symptoms was from six months to eighteen years. In 21 cases it was longer than three years; the duration was not given in 3 cases. No case of acute fulminating hemorrhagic purpura has been reported in which splenectomy was attempted. Of the 28 patients only 8 are known to be males; in 3 cases the sex was not given. The youngest patient was three years, the oldest fifty-three. All the others were younger than thirty-six, and 18 were younger than twenty-five years; the ages of 4 were not recorded. The disease is predominantly one of youth and adolescence.

The Spleen. In 4 of the 28 cases the size of the spleen is not mentioned, while in 15 of the remaining 24 it was palpable; in 9 it was not palpable. Usually it appeared to be only slightly enlarged. It is quite evident that palpability or even enlargement of the spleen is not essential to the decision for splenectomy. In 15 cases the weight of the spleen is given; in 1 it was 1400 gm.; in the remaining 14 cases it averaged 204 gm. In 1 case, that of an adult aged twenty-two years, it weighed only 92 gm. The spleen in children was slightly larger in proportion to their weight than the spleen in adults. In our cases the weight of the spleen was less than would have been expected in the consideration of its apparent size on physical examination, probably indicating that the organ in purpura hemorrhagica contains a large quantity of blood. The pressure exerted at the time of operation would be expected to reduce considerably the size of a vascular organ.

The Operation and Mortality. No difficulty with excessive bleeding has been encountered immediately following operation. The excessive oozing at operation disappears promptly after the spleen is removed. Transfusions have been necessary in a few of the cases, before, during, or after operation chiefly as a supportive measure. Two operative deaths occurred, 1 reported as a "heart death" at the time of operation, the other following subphrenic abscess. In the other cases convalescence has been very rapid and satisfactory.

Postoperative Bleeding. In 6 of the 26 cases slight epistaxis occurred chiefly during the first few days after operation. In Case III slight epistaxis occurred at times for five months following operation, the platelets were still low, but no other form of bleeding appeared and the patient was reported as well five years later. In Case V slight epistaxis occurred twenty-one days after operation. In Case XIII petechiæ appeared five months after operation, but were transient. In Case XIV epistaxis accompanied catarrhal jaundice one to three months after operation. In Case XVI occasional crops of petechiæ appeared for a month following operation. In Case XXIII petechiæ accompanied an acute respiratory infection one month after operation. Petechiæ appeared after convalescence in 2 cases. In Case XXI they appeared one year after operation after three days' severe reaction following vaccination, and cleared up promptly. In all cases, so far as can be ascertained, these slight evidences of the hemorrhagic tendency were transient. Their appearance suggest the possibility that foci of infection might still be present in these cases. The logical procedure in cases of purpura hemorrhagica would seem to be splenectomy followed by elimination of all possible foci; the latter portion of the treatment cannot be safely neglected.

The Platelets. In most of the cases before operation, at some time in the course of each case, the platelets numbered less than 50,000. The platelet level before operation in cases in which multi-

ple counts are recorded was below 100,000, except for occasional short periods, usually days, in which the platelets might rise approximately to normal. In Case V at one time no platelets were found. In a few instances the counts were in the hundreds.

After operation the platelets almost always rose rapidly to above normal, and in three instances more than 1,000,000 are recorded. In two instances they remained below 50,000 but even in these cases the ultimate results were satisfactory. In 6 cases after a rise in the platelet count, a subsequent fall below 50,000 is noted. Active bleeding did not recur, although petechiæ and epistaxis were sometimes present when the platelets became reduced. However, transient petechiæ and epistaxis occurred also in some of the cases in which the platelets were not reduced. These facts indicate that the increased number of the platelets is only one factor in the arrest of purpuric manifestations. It is well known that the platelets are morphologically abnormal in this disease, and more or less complete recovery from this would be likely to influence the clinical result. A study of the morphology of platelets by means of the ultramicroscope may be expected to add to the information on this subject.

In 8 cases the platelet counts were made from two to eight hours after splenectomy; they varied from 17,000 to 202,000, while in 7 cases they were over 50,000 and in 3 over 100,000. This rapid rise of the platelets within a few hours of splenectomy is almost as striking as the cessation of bleeding. In almost all instances the platelet counts made one day after operation were more than 100,000. The highest counts are usually recorded between the sixth and the ninth days, although in four instances they were recorded on the second and third days, and in one instance as late as the twenty-first day. In Case XVI the count did not rise above 31,200 during convalescence.

More platelet counts over a long period of time are necessary after splenectomy to determine the postoperative platelet level. The data at hand indicate that frequent counts before operation show a platelet level below 100,000 with occasional elevations above this even up to normal, and following operation the maintenance of a higher level with occasional depression below 100,000 except in the occasional case in which the platelet level may remain low for longer periods of time.

The Tourniquet Test. This test was always positive when applied during active periods of purpura and not infrequently during remissions. After operation it became negative soon after the petechiæ and ecchymoses faded.

The Bleeding time and Retractility of Clot. Two and a half minutes or less may be regarded as a normal bleeding time. In many of the cases the bleeding time was longer than eight minutes and occasionally longer than one hour, although not infrequently it was approximately five or six minutes. After splenectomy there

was great variability in the promptness with which the bleeding time became reduced. In 3 cases it is reported as normal within a few hours. In most of the cases it became reduced quite promptly

FINDINGS IN REPORTED CASES OF THROMBOCYTOPENIC PURPURA HEMORRHAGICA.

Case.	Author.	Date of operation.	Sex.	Age, yrs.	Duration before operation., yrs.	Platelets.		Weight of spleen. mg.	Last report after operation, mos.	Remarks.
						Before operation.	After operation.			
I	Kaznelson	1916	F.	36	10	600	500,000	..	60	No recurrence; well.
II	Kaznelson	1916	F.	25	5	700	408,000 20,000	250	60	Slight epistaxis; well.
III	Kaznelson[1]	1915	F.	11	3	6700	267,000 13,000	..	60	Slight epistaxis for 3 mos.; well.
IV	Benecke	1917	F.	20	3+	38,370	1,783,514	..	3	No recurrence.
V	Ehrenberg	1918	F.	19	Several	None found	684,700 13,000	..	..	No recurrence.
VI	Minkowski	1919	M.	53	2½	14,000	100,000	..	2	Slight epistaxis 21 days after opera.; good result.
VII	Minot	1920	..	..	10	10,000	300,000	..	24	No recurrence.
VIII	Kaznelson	1921	..	..	..	...	...	..	..	"Heart death" at operation.
IX	Kaznelson	1921	F.	..	..	38,000	550,000	..	Recent	No recurrence.
X	Retzlaff	1921	..	..	..	Details	not given	..	..	No recurrence.
XI	Cori	1921	F.	15	4	2200	743,000 23,000	..	10	No recurrence.
XII	Cori	1921	F.	21	Several	Very low	1,150,000	320	1	No recurrence; death; subphrenic abs.
XIII	Steinbrinck	1921	F.	3	1	700	10,000 40,000	..	6	Petechiæ 5 mos. after operation; good result.
XIV	Bowen	1922	M.	22	18	2500	17,000 608,000	..	4	Catar. jaundice with epistaxis 1 to 3 mos.; good result.
XV	Brill and Rosenthal	1922	F.	19	14	6800	290,000 10,000	1400	4	No recurrence.
XVI	Brill and Rosenthal Rosenthal	1922	M.	15	3½	400 24,000	31,200 10,000	300	4	Petechiæ for 1 mo. good result.
XVII	Hitzrot	1923	F.	8	3	4000	50,000 600,000	120	3	No recurrence.
XVIII	Wild	1922	M.	15	Several	Not given	92,500 1,033,000	340	9	Emergency; a spontaneous rupture of the spleen; no recurrence.
XIX	Cohn and Lemann	1923	M.	5	½	Few	200,000	..	6	Chiefly purpura before opera. no recurrence after opera.
XX	Mayo Clinic	1923	F.	31	1½	24,000	727,000	210	19	No recurrence.
XXI	Mayo Clinic	1923	F.	23	13	54,000	638,000	200	12	No recurrence.
XXII	Mayo Clinic	1924	M.	24	12	72,000	280,000	220	8	No recurrence.
XXIII	Mayo Clinic	1924	F.	11	5	46,000	430,000 50,000	168	7	Sl. recurrence with cold 6 wks. after op., none since.
XXIV	Mayo Clinic	1924	M.	32	2	36,000	816,000	164	5	No recurrence.
XXV	Mayo Clinic	1924	F.	11	5	54,000	780,000 88,000	202	5	No recurrence.
XXVI	Mayo Clinic	1924	F.	15	10	42,000	516,000	125	5	No recurrence.
XXVII	Mayo Clinic	1924	F.	18	15+	42,000	840,000	92	5	No recurrence.
XXVIII	Mayo Clinic[2]	1925	M.	27	1	52,000	504,000	140	3	No recurrence.

[1] Schmidt reported 2 cases which seem to be identical with those reported by Kaznelson.
[2] New case.

to less than eight minutes, and in from five to eighteen days to less than three minutes. In Case XIII the bleeding time, however, was forty-one minutes nine weeks after operation. Still greater variability is shown in the retractility of the clot. In 2 cases retractility was satisfactory within a few hours of operation, in another it was absent in fifteen days. In Case XV clot retraction was present the first month, absent the second, and present the third month. Apparently the recovery of this function is likely to be delayed longer than that of the other factors of coagulation. However, the test for retractility has not yet been standardized, and some of the unsatisfactory results may be due to this fact.

The Pathologic Condition of Extirpated Spleens. A detailed description of the condition of spleens removed at operation cannot be undertaken in this paper. In general, it has been noted that spleens removed in the Mayo Clinic cases are vascular, and usually soft, and show nothing of outstanding importance either grossly or microscopically except the presence of an abnormally large number of neutrophilic polymorphonuclear leukocytes. It would seem appropriate to say that the splenomegaly of this disease is an acute splenitis.

Conclusions. The recurrence of petechiæ in some of the cases, the slowness with which the bleeding time becomes reduced, and the variability in connection with the rcovery of the retractility of the clot, indicate that although a change has been brought about by splenectomy sufficient to arrest gross hemorrhage, the finer mechanism of coagulation requires a complex readjustment on the part of the organism, which may or may not become complete and permanent. A few of the patients have remained somewhat anemic. However, the uniformly good results indicate at least a temporary cure.

So far as is known at present, only well defined cases of purpura hemorrhagica should be recommended for splenectomy. A correct diagnosis, therefore, becomes especially important. Aplastic anemia with hemorrhagic features may be most difficult to differentiate from hemorrhagic purpura. A persistent and extreme leukopenia and a low reticulated cell count are a characteristic of aplastic anemia, and the period of bleeding has been preceded by a period of rapidly developing anemia. Borderline conditions also occur with confusing coagulation features in which a decision between hemophilia and hemorrhagic purpura is impossible.

More frequent estimations of the platelets and the various features of coagulation both preceding and following splenectomy, standardization of the test for the retractility of the clot, and an understanding of the morphologic and chemical abnormality of the platelet and the function of the spleen in relationship to the destruction of platelets, are especially important matters for immediate study.

Since the preparation of this paper 6 other cases have been reported in the literature, 2 by Ricaldoni and Albo, 2 by Sutherland and Williamson, 1 by Bass and Cohn, and 1 by Flexner. These are typical cases, and in general the results of splenectomy correspond to those observed elsewhere. Another borderline case, with some signs of an acute myelosis, has been reported by Mitchell and Farley. The fatal outcome a few weeks after splenectomy was preceded by considerable symptomatic improvement, and a partial high intestinal obstruction must at least be considered a factor in the unfavorable result.

BIBLIOGRAPHY.

1. Bass, M. H., and Cohen, Philip: Thrombocytopenic Purpura Hemorrhagica Successfully Treated by Splenectomy, Am. Jour. Dis. Child., 1924, **27**, 333.

2. Benecke, Elizabeth: Hæmorrhagische Diathese (essentielle Thrombopenie) durch Milzextirpation geheilt, Therap. Gegenw., 1917, **9**, 418.

3. Bowen, B. D.: A Case of Chronic Purpura Hemorrhagica with Therapeutic Splenectomy, Bull. Buffalo Gen. Hosp., 1923, **1**, 2.

4. Brill, N. E., and Rosenthal, N.: The Treatment by Splenectomy of Essential Thrombocytopenia (Purpura Hemorrhagica), Trans. Assn. Am. Phys., 1923, **38**, 294; The Curative Treatment by Splenectomy of Chronic Thrombocytopenic Purpura Hemorrhagica, Am. Jour. Med. Sci., 1923, **166**, 503.

5. Cohn, I., and Lemann, I. I.: Splenectomy as a Treatment for Purpura Hemorrhagica, Surg., Gynec. and Obst., 1924, **38**, 596.

6. Cori, G.: Zur Klinik und Therapie (Splenektomie) der essentiellen Thrombopenia, Ztschr. f. klin. Med., 1922, **94**, 356.

7. Ehrenberg, Charlotte: Ueber einen Fall von essentieller Thrombopenie und seine Behandlung durch Milzextirpation, Monatschr. f. Geburtsh. u. Gynäk., 1920, **51**, 99.

8. Flexner, M.: Idiopathic Purpura Hemorrhagica, with a Report of a Case Cured by Splenectomy, Kentucky Med. Jour., 1925, **23**, 56.

9. Giffin, H. Z.: Discussion: The Treatment of Splenectomy of Essential Thrombocytopenia (Purpura Hemorrhagica), Trans. Assn. Am. Phys., 1923, **38**, 314.

10. Giffin, H. Z., and Holloway, J. K.: Hemorrhagic Purpura, Med. Clin. North America, 1923, **7**, 241.

11. Giffin, H. Z.: Splenectomy in Cases of Purpura Hemorrhagica, Minnesota Med., 1925, **8**, 207.

12. Hitzrot, J. M.: Splenectomy in Hemorrhagic Purpura, Ann. Surg., 1923, **78**, 185.

13. Kaznelson, P.: Verschwinden der hämorrhagischen Diathese bei einen Falle von "essentieller Thrombopenie" (Frank) nach Milzexstirpation, Splenogene Purpura, Wien. klin. Wchnschr., 1916, **29**, 1451; Purpura, Wien. klin. Wchnschr., 1916, **29**, 1451; Thrombolytische Purpura, Ztschr. f. klin. Med., 1919, **87**, 133; Beiträge zur Pathogenese hämorrhagischer Diathesen, III, Deutsch. Arch. f. klin. Med., 1919, **128**, 119; Beobachtungen über paroxysmale Kältenhämoglobinurie und Kälteikterus, Deutsch. Arch. f. klin. Med., 1921–1922, **138**, 46.

14. Mayo, W. J.: The Splenomegalies, Boston Med. and Surg. Jour., 1924, **190**, 1.

15. Minkowski, O.: Hæmorrhagische Diathese, Thrombopenie und Milzfunktion, Med. Klin., 1919, **2**, 1243, 1279.

16. Minot, G. R.: Discussion, Trans. Assn. Am. Phys., 1923, **38**, 314.

17. Retzlaff: Quoted by Kaznelson, 1921–1922.

18. Ricaldoni, M. A., and Albo, M.: Purpura chroniques sans splénomégalie guéris par la splénectomie, Bull. et mém. Soc. méd. d. hôp. de Paris, 1924, **40**, 493.

19. Steinbrinck, Walter: Ein Beitrag zur Thrombocytenfrage, Ztschr. f. klin. Med., 1922, **94**, 447.

20. Sutherland, G. A., and Williamson, Bruce: The Treatment of Purpura Hæmorrhagica by Splenectomy, Lancet, 1925, **208**, 323.

21. Wild, Ernst: Hæmorrhagische Diathese (essentielle Thrombopenie Frank) geheilt durch Milzexstirpation nach Spontanruptur, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1923, **37**, 201.

A CLINICAL STUDY OF QUINIDIN THERAPY.

Report of Fifty-two Cases of Auricular Fibrillation with Restoration of the Normal Rhythm in Seventy-nine Per Cent.

By Herman H. Riecker, M.D.,
NEW YORK CITY.

(From the First Medical Division of the New York Hospital and the Department of Medicine of the Cornell University Medical School.)

The introduction of quinin as a therapeutic agent in the treatment of certain phases of heart disease by Wenckebach ten years ago, and its more practical application as quinidin by Frey in 1917, has led to many and varied estimations of its value, considerable experimentation to account for its action, particularly by Lewis, and divergent results from its clinical application. Hitherto quinidin has perhaps yielded far more brilliant results in the experimental study of the nature of auricular fibrillation than in the treatment of that condition, but there seems reason to believe that this is true only because our technic of the use of quinidin as a therapeutic agent is still far from being perfected and standardized. For this reason an analysis of the results, being obtained by means of a standard method of treatment of an unselected group of cases, should be of distinct value.

The general opinion concerning the use of quinidin in auricular fibrillation seems to be that under favorable conditions the fibrillation is converted to a sinus rhythm in about 50 per cent of the cases, notably those with a recent onset. Furthermore, it has been generally reported that the duration of the regular rhythm frequently has been short, such as to confer no real benefit to the patient, who perhaps may assume the risk of a fatal termination of his disease by the accident of embolic phenomena or of respiratory paralysis. The experience obtained during the treatment of the 52 cases which compose this study has not been such as to confirm this general impression, but rather leads to a more optimistic attitude toward the use of quinidin in auricular fibrillation.

The object of this paper is to describe in detail the method of treatment of auricular fibrillation with quinidin, which is being used in the First Medical Division of the New York Hospital, and to discuss the results obtained.

While as a whole these results are not remarkable, because of the several failures which occurred during our earlier experience with quinidin therapy, those more recently obtained seem to be sufficiently successful to justify their publication. The plan of treatment now in use is the result of experience obtained during the past three

years with quinidin in 52 cases of chronic heart disease complicated by the presence, over a considerable period, of auricular fibrillation.

The more important theoretical considerations involved in the use of quinidin must be thoroughly appreciated in order to understand the rationale of the therapy. Lewis[1] has shown that in the fibrillating heart, under the influence of quinidin, the rate of the auricular oscillations is slowed, and the ventricular rate increased, until in certain cases the lengthening of the refractory period over the conduction time abolishes the circus movement and the pacemaker resumes its function.

It has been noticed that quite often during quinidin administration the ventricular rate reaches such a height that the drug must be withdrawn before definite therapeutic effects have been obtained. As a means of preventing this, advantage is taken of the action of digitalis in fibrillation, since it effects a block at the auriculoventricular junction and prevents the weaker impulses arising in ectopic foci in the auricle from causing ventricular contraction. By the use of digitalis in large doses the acceleration of the ventricular rate which sometimes occurs during quinidin treatment may be counteracted, and one of its most unpleasant effects avoided. It has been suggested that the action of quinidin may be impeded[2, 3] by the simultaneous use of digitalis because it is known that the latter drug sometimes increases the rate of fibrillation in the auricle. However, Lewis[4] maintains that "The slight disadvantage to the quinidin reaction which follows from simultaneous digitalis therapy is often more than counterbalanced by the control of the ventricular rate which is obtained." The latter view is certainly substantiated by the results in the present series of cases, although occasionally quinidin alone will effect a reversion of the rhythm. Conditions which tend to accelerate the heart rate, such as exercise or mental excitement or fever, must be avoided during the administration of quinidin because they tend to relieve the delayed conduction time established by digitalis and thus defeat its purpose in that respect.

The plan of treatment consists in the preliminary thorough digitalization of the patient, complete rest in bed and other measures if necessary, to bring his heart to the best possible degree of compensation. The common criteria are used to estimate the condition of the circulation, such as the slowing of the apex rate, a decrease in the pulse deficit, loss of edema and congestion as far as possible, and an increase in the vital capacity. The heart rate should be reduced to 60 to 80 beats per minute, and should not fluctuate materially during any twenty-four-hour period. To facilitate the action of digitalis all exercise should be prohibited, mental excitement guarded against, and finally the presence of fever avoided if possible, before beginning the administration of quinidin. It has been noted in the study of these cases that the quinidin treatment of fibrillation was seldom successful when the patient was permitted

to be out of bed, or when the drug was administered during a febrile period, concomitant with a rise in the pulse rate; the need for avoidance of these factors cannot be too strongly emphasized. It is the careful attention to the details of treatment which may bring success in cases somewhat resistant to the effects of the drug.

When the general condition of the patient has been improved as much as possible by means of rest and digitalis therapy the use of this drug is discontinued temporarily, and the administration of quinidin begun within twenty-four hours. The method of administering quinidin itself is of such importance that it deserves special emphasis. Quinidin sulphate is given in capsules in 0.4 gm. doses every four hours day and night. Lewis[5] has made a study of the changes in the auricular and ventricular rates produced by a single dose of quinidin, and has found that the heart recovers from the effect of the drug in such a short time that it must be given at frequent intervals. According to this investigator, a depression of the auricular oscillations must be maintained at a rate of 250 to 300 per minute in order to secure a reversion of the rhythm. If the drug is not given at night the effect of the previous day's administration will have been lost by the following morning. The necessity of administering the drug continuously throughout the night as well as the day is apparent and, indeed, failure at times to restore the fibrillating heart to the normal rhythm may be ascribed to this omission. If the normal sinus rhythm is attained without the appearance of untoward symptoms quinidin is withdrawn within twenty-four hours and digitalis given in maintenance doses, usually about 30 minims of the tincture per day, if necessary.

In 2 recent cases (Nos. 196 and 359) the usual dosage of quinidin had no effect on the rate or rhythm of the heart and did not cause symptoms of cinchonism. The dosage was then doubled, 0.8 gm. being given every four hours, and after a few doses the heart rate became regular in each case. It seems therefore that all cases do not react to the same concentration of the drug in the body, and that the reaction of the patient alone should be the final guide as to the amount of quinidin which may be given in a single dose.

All the cases upon which this study is based have been chronic auricular fibrillation, and in by far the greater number there has been the definite valvular damage of rheumatic endocarditis. In 52 consecutive cases treated with quinidin on this service there were 41, or about 79 per cent, in which the normal sinus mechanism was restored. Of these 41 cases it is known that in 6 the heart had remained regular for more than a year, and in 12 for more than six months. Six additional cases have maintained a sinus rhythm for more than three months. Many of the cases are still under observation and many of the remaining (beside the 24 here accounted for) we have been unable to follow. In 11 cases quinidin as given did not restore the sinus rhythm. Several of

these were treated under unfavorable circumstances, and before the method had become standardized.

Failure to respond to treatment may be determined in a large percentage of the cases from a study of their records. The causes of failure fall into two general groups: (1) Faulty administration of either digitalis or quinidin or both, and (2) improper management of the cases with reference to exercise or mental excitement or the presence of fever. In the first group there are cases in which digitalis was either not employed at all or given in insufficient amount to produce the desired effect, and several times the rapid ventricular rate resulting from a few doses of quinidin made the patient so uncomfortable (because of the rapid rate) that the drug had to be withdrawn before the normal sinus rhythm could have been established. This applies particularly to the early cases. In many successfully treated cases a moderate ventricular acceleration occurred, lasting for several hours after the discontinuance of the drug, while in others the rate was depressed. In 1 case the rate upon resumption of the normal rhythm was 50 beats per minute. This resulted after 4.8 gm. of quinidin had been given during twenty-four hours. In 1 unsuccessful case (No. 194) quinidin had no effect on the rate, nor did it cause symptoms of cinchonism, and it is probable that not enough of the drug was given in each dose. In the second group of unsuccessfully treated cases several patients were out of bed, and several had a slight fever at the time of the administration of quinidin. These factors tend both to destroy the blocking effect of digitalis on the ventricular rate, and to hinder the improvement of the general circulation. A study of the case records shows that an essential point was to keep the patient at absolute rest in bed. With few exceptions, in all the cases in which the quinidin treatment was successful the rules outlined above were carefully adhered to, and with similar exceptions all the cases which failed to respond to the drug showed by their charts that the above conditions were not followed. There were 3 cases in which no specific reason could be assigned for the failure of quinidin to restore the rhythm. Separate consideration must be accorded 2 cases in which the fibrillation was converted to a flutter under the influence of quinidin (Nos. 330 and 356). These 2 reverted to fibrillation under the influence of digitalis and are classed as unsuccessfully treated cases.

In thyrotoxicosis complicated by cardiac decompensation and auricular fibrillation quinidin treatment is definitely indicated. In this series there are 7 such cases and in all the sinus rhythm was restored. In 3 of the cases the return to normal rhythm was transitory, but in the remaining 4 a regular mechanism has been maintained for periods of six, five, four and two months respectively. From this small series general conclusions cannot be safely drawn with regard to their management. It may be, however, that in

the preoperative preparation of this type of patient a regular heart rhythm improves the surgical prognosis, and in our experience can be easily attained.

In the study of the electrocardiograms of the successfully treated cases it was noted that the *P–R* interval was prolonged in all those in which the sinus rhythm persisted for any considerable period of time. At the time of the resumption of the normal rhythm the *P–R* intervals varied between 0.18 and 0.34 second. These cases divide themselves into two groups: One in which it seemed that

Case No.	Date of admission.	Degree of decompensation.	Duration of fibrillation, months.	Amount digitalis before quinidin, drams.	Amount quinidin before revision, grams.	Pulse rates.		*P–R* intervals second.	Duration of restored rhythm, months.	Remarks.
						Before quinidin.	After restored rhythm.			
296	8/22	Marked	4	5	0.4	80	200	0.24	26	
139	3/22	Moderate	18	5	2.4	68	68	0.28	28	
308	1/23	Marked	12	8½	2.4	64	88	0.32	18	
168	7/23	Marked	18	12	4.2	64	64	0.22	12	
280	1/22	Marked	24	1	0.8	66	118	0.20	12	
325	7/23	Marked	24	7	1.6	72	80	0.30	10	
270	7/21	Moderate	12	2	6.0	64	70	0.20	6	
176	1/22	Marked	24	2	14.4	88	100	0.24	6	
202	2/24	Moderate	2	8	2.0	76	76	0.20	6	
195	7/24	Moderate	7	8	0.8	80	102	0.24	4	
124	11/21	Marked	12	3	3.0	92	80	0.21	6	
130	3/22	Marked	4	2½	3.0	80	88	0.21	6	
169	2/23	Slight	3	9	5.0	76	92	?	3	
288	3/22	Marked	3	11	1.6	78	80	0.18	12	
129	3/22	Slight	1	2½	3.2	68	68	0.18	1	
146	7/22	Slight	3	4	0.4	88	88	0.20	1	
349	1/24	Moderate	3	5	5.0	96	96	0.32	6	
345	12/23	Slight	1	6	3.6	88	88	0.24	3	
337	10/23	Moderate	4	7½	0.8	72	72	0.20	6	
351	2/24	Moderate	12	9	3.2	72	72	0.22	3	
95	8/23	Slight	?	5	2.8	96	96	0.20	3	
10	11/22	Moderate	6	5	1.6	100	100	0.18	6	Thyrotoxicosis.
11	10/22	Marked	6	25	2.0	96	96	0.16	2 days	Thyrotoxicosis.
17	1/22	Slight	?	3	3.2	98	82	?	Few days	Thyrotoxicosis.
9	3/24	Marked	?	10	0.6	82	82	0.20	½	Thyrotoxicosis.
45	7/24	Moderate	6	10	0.8	94	80	0.20	5	Thyrotoxicosis.
357	3/24	Marked	3	9	1.6	64	84	?	2	Thyrotoxicosis.
360	10/24	Marked	6	11	2.4	80	78	0.20	1	Thyrotoxicosis.
190	4/24	Moderate	24	6	4.4	72	100	0.18	7	
869	5/24	Slight	1½	3	2.0	70	104	0.20	5	
184	11/23	Slight	6	2	1.6	64	72	0.18	1	
297	5/22	Marked	6	10	1.6	86	102	0.22	Few days	
266	7/21	Marked	12	5	2.0	72	100	?	1	
259	5/21	Slight	36	0	6.6	50	74	?	1	
166	1/23	Marked	8	10	1.6	72	84	?	½	
196	7/24	Moderate	2	7½	3.2	76	102	0.24	4	
358	8/24	Moderate	4	3	4.0	68	80	0.22	2	
359	10/24	Marked	24	6	2.4	58	64	0.22	1	
361	10/24	Slight	12	7	4.0	80	84	0.22	1	
362	10/24	Moderate	12	5	4.0	72	80	0.24	1	
363	11/24	Slight	12	3	5.6	48	52	0.26	1	
134	5/22	Marked	36	8	10.0	76	Unsuccessful			
178	4/23	Moderate	8	10	19.0	60	Unsuccessful			
330	7/23	Marked	2	10	15.0	56	Unsuccessful		....	Auricular flutter.
331	9/23	Moderate	4	6	17.0	70	Unsuccessful			
285	1/22	Marked	24	3	17.0	90	Unsuccessful			
265	5/21	Slight	6	8	4.2	72	Unsuccessful			
143	7/22	Marked	4	0	1.6	72	Unsuccessful			
148	8/22	Marked	24	9	5.0	76	Unsuccessful			
164	6/23	Moderate	3	3	5.0	64	Unsuccessful			
194	7/24	Moderate	48	6	6.0	72	Unsuccessful			
356	6/24	Marked	3	7	5.0	46	Unsuccessful		....	Auricular flutter.

there was a previous pathologic partial heart block which of course persisted after the resumption of the regular rate, and was independent of drug therapy; the other in which a prolonged conduction time had been maintained by the continuous administration of digitalis. It is noteworthy that those which quickly reverted to a fibrillation usually had the shorter *P–R* interval (Cases Nos. 129, 146, 11, 17 and 184). While the reverse is not altogether true, that the greater the *P–R* interval the longer the duration of the sinus rhythm, it so happens that in the cases in which the heart has remained regular for more than a year a markedly delayed conduction time was found to have been present (Cases Nos. 296, 368, 349 and 308). The significance of this observation is not to be emphasized, with respect to its prognostic value, until further observations can be made of all the factors concerned. The appearance of a prolonged conduction time after the restoration of the rhythm has been noted by others.[6, 7]

There was no relationship in this series of cases between the amount of quinidin used to convert the rhythm (nor the amount of digitalis used previously) and the degree of heart block found to be present after the normal sinus rhythm had been established. It is quite remarkable that the total amount of quinidin needed to convert the fibrillation to a sinus rhythm in most cases was quite small. In only 2 of 41 successfully treated cases were more than 5 gm. of quinidin used, and in 25 cases not more than 3 gm. of the drug were used to restore the rhythm. It appears from this experience that the probability of success diminishes very rapidly after more than 5 gm. of the drug have been given.

Much has been written with regard to contraindications to the use of quinidin. Those usually heeded are: (1) Special sensitiveness to the physiologic action of the cinchona compounds; (2) a recent history of embolic phenomena; (3) marked decompensation of the heart. All cases on this service have been treated with the drug in which at least a moderate degree of compensation could be obtained, without regard to the duration of heart disease. In a few exceptional cases quinidin was given in the presence of a considerable degree of decompensation and with excellent results. There was but 1 case in this series to which the drug could not be given because of cinchonism, and in no case did the conversion of auricular fibrillation to the normal sinus rhythm give rise to signs of embolism. In 1 case (No. 129) it appeared that quinidin caused a respiratory paralysis which was fortunately transient. This patient was a man, aged sixty years, who during the administration of quinidin suddenly became unconscious, but gradually revived and his heart rate remained regular. Frey,[8] among others, has reported a similar case.

In many instances it was difficult to determine definitely the length of time that fibrillation of the heart had existed before the

patient entered the hospital, but this factor is not regarded as of much prognostic value with reference to successful treatment. Many of the early papers on quinidin therapy emphasized the point that in long standing cases of fibrillation the normal heart rhythm could not usually be restored. The study of this series of cases does not substantiate that impression, and it seems that other factors than duration of fibrillation must play a part in the failure of treatment in this group of patients. Neither the kind of heart disease nor the amount of decompensation which the patient had experienced seemed to have any relation to success or failure of treatment so far as could be determined.

The maintenance of the sinus rhythm after its restoration by quinidin is a matter of the greatest importance because upon this depends the ultimate benefit which the patient may derive. Provided other things are equal, fibrillation in heart disease offers a shorter life expectancy than does a regular rhythm, and it usually curtails the patient's activities. In quinidin treatment more progress has been made, and less confusion exists, with regard to the actual restoration of the normal rhythm than to the maintenance of it, although the latter problem is of equal importance. The experience gained in the after treatment of this series of cases makes one feel not so sure that the administration of quinidin in the smallest effective dosage is the essential therapy in order to prevent the recurrence of fibrillation, as has been suggested.[9, 10]

There was noted several times in the follow-up of the early cases in this series a succession of events as follows: The heart rate was lowered and the general circulation improved by the use of digitalis, and quinidin caused a restoration of the normal rhythm. The patient was allowed out of bed, quinidin continued in smaller doses, but no digitalis given. Then the heart rate gradually increased, and in a short time fibrillation of the auricles appeared. Experience so far seems to indicate that the use of digitalis in the after treatment of these cases is even more important than that of quinidin, but the problem is far from being solved. It is obvious that the use of digitalis tends to counteract and overcome the original factor which probably caused the auricles to fibrillate, namely, a weakened, diseased and overtaxed myocardium.

The accompanying table is made up of the essential information concerning the points which are emphasized in the paper. In some instances the time given for "probable duration of fibrillation" could only be estimated from the histories; many of the successfully treated cases we have been unable to follow in the metropolitan district of New York, and several cases have only recently been discharged from the hospital. The P–R intervals are those measured on Lead II of the electrocardiograms, and these were usually taken quite soon after the return of the normal mechanism. With few exceptions, electrocardiograms were taken of all

cases before and after the treatment with quinidin in order to detect the occasional appearance of auricular flutter with apparently regular ventricular rhythms, or when complete dissociation occurs with fibrillating auricles.

I am greatly obligated to Dr. Lewis A. Conner and Dr. Nellis B. Foster for their invaluable assistance in the study of these cases and in the preparation of the paper.

Conclusions. 1. The use of quinidin sulphate is justified and seems indicated in all cases of auricular fibrillation, except in those in which there are signs of recent embolism, marked decompensation of the heart or early appearance of the symptoms of cinchonism.

2. Both the temporary and permanent conversion of the fibrillation to a normal sinus rhythm by the drug seems to be favorably influenced by the presence of a delayed conduction time at the auriculoventricular junction.

3. The careful management of cases with regard to exercise, mental excitement and fever during quinidin administration greatly facilitates the favorable action of the drug.

4. The administration of quinidin is most effectual when given continuously through the day and night as suggested by the work of Lewis.

5. The use of digitalis to maintain the rhythm after its conversion seems to be even more important than that of quinidin in chronic auricular fibrillation.

REFERENCES.

1. Lewis, Drury, Illiescu, and Wedd: Heart, 1921, **9**, 55.
2. Levy, R.: Proc. Soc. Exper. Biol. and Med., 1921, **19**, 88.
3. Hamburger and Priest: Jour. Am. Med. Assn., 1922, **79**, 3, 187.
4. Lewis et al.: Heart, 1922, **9**, 207.
5. Lewis, T.: Am. Jour. Med. Sci., 1922, **163**, 781.
6. Viko, Marvin and White: Arch. Int. Med., 1923, **31**, 545.
7. Wolferth, C. C.: Am. Jour. Med. Sci., 1921, **162**, 812.
8. Frey: Deutsch. Arch. f. klin. Med., 1921, **136**, 70.
9. Korns: Arch. Int. Med., 1923, **31**, 45.
10. Wybauw: Arch. d. mal. d. Coeur., 1922, **15**, 206.

EXPERIMENTAL GASTRIC AND DUODENAL INFLAMMATION AND ULCER.

Produced with a Specific Organism Fulfilling Koch's Postulates.

By Albert Hoffmann,

Johnston-Wickett Clinic, Anaheim, Calif.

The object of this paper is to give a preliminary report of my findings and to describe the morphology, isolation and recovery,

FIG. 1.—Guinea pig No. 105. Lesions confined to stomach. This animal received 2 cc. of toxin (intracardiac) and was killed by ether forty-eight hours afterward.

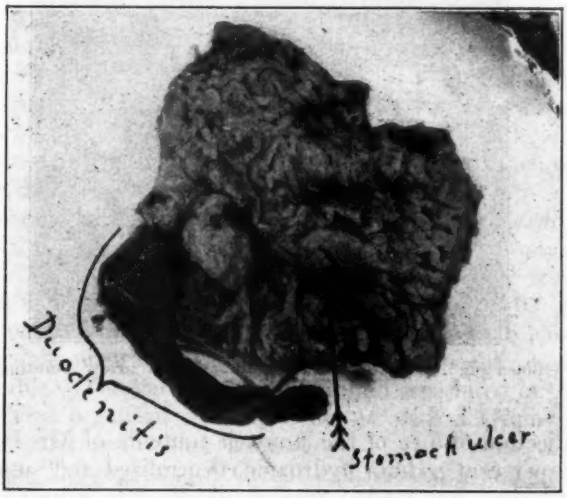

FIG. 2.—Guinea pig No. 3. Stomach and duodenum, showing ulcer in gastric mucosa and duodenitis.

cultural characteristics and pathogenicity, in the guinea pig, of an organism from the stomach contents of 2 patients, diagnosed as having gastric or duodenal ulcer, and from tonsil emulsion of a third patient, who also was diagnosed as having gastric or duodenal ulcer.

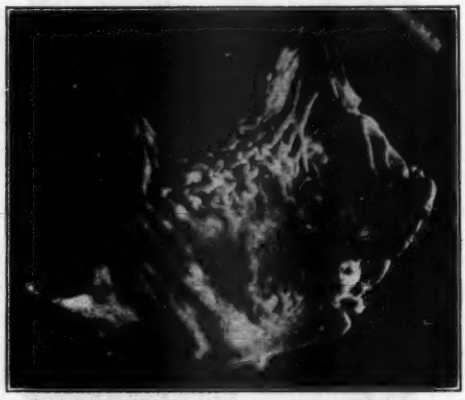

FIG. 3.—Guinea pig No. 102. Showing triangular ulcer at pyloric end of the gastric mucosa.

With material from these 3 known human ulcer cases I was able to reproduce lesions in the guinea pig, from which lesions the specific organism was isolated.

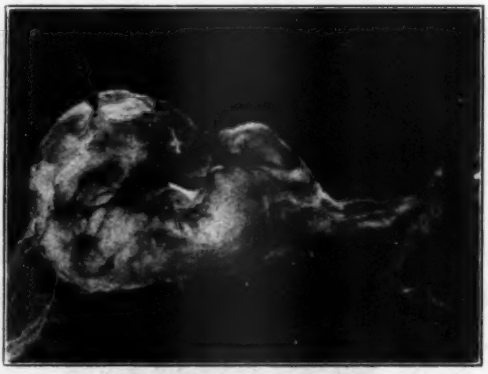

FIG. 4.—Guinea pig No. 17. Showing stomach with arrow pointing to minute perforating ulcer.

An injection of 5 cc of the stomach contents of Mr. H. (treated with 10 per cent sodium hydroxide, neutralized and suspended in saline solution) was made intraäbdominally into guinea pig No. 1. The lesions diagnosed in the case of Mr. H. were reproduced in this guinea pig, and from these reproduced lesions the specific

organism was isolated. This organism was then injected, either in washings from agar slants or in glucose broth media (see table), into guinea pigs Nos. 2, 3, 4, 9, 10, 12, 16 and 17. This specific organism was subsequently recovered from the specific lesions in Nos. 2 and 3. No. 4, a small animal, died after eight hours; the specific lesions were reproduced in this instance, but an effort to recover the organism was not practicable. The specific lesions were also reproduced in Nos. 9, 10, 16 and 17. In the case of No. 12 the animal died of hemorrhage in the thorax. Pressure of other duties precluded any effort to recover the specific organism from Nos. 9, 10, 12 and 16. In the case of No. 17 I preferred not to disturb the specimen. Bacterial filtrate, forty-eight hours old, from the specific organism isolated from No. 1, upon being injected (4 cc intra-abdominally) into No. 11, also reproduced the specific lesions.

The specific organism recovered from No. 3 reproduced the specific lesions in No. 5, but was not in turn recovered from No. 5, the attempt not being made because of pressure of other duties. However, bacterial suspension (forty-eight hours old) from the bacillus that had been recovered from No. 3 reproduced in No. 6 the specific lesion, with myositis at the point of inoculation, which was done intramuscularly. The specific organism was recovered from the specific lesion in No. 6.

The complete tonsils of Mr. N. were emulsified with 10 per cent sodium hydroxide. The emulsion was neutralized and (after being washed with normal saline solution) 3 cc of it was injected intra-abdominally and intramuscularly in No. 7. In this animal the specific lesions were reproduced (with myositis), and the specific organism was recovered from these lesions.

Two cubic centimeters of the stomach contents of Mr. L. was injected intraäbdominally and intramuscularly into guinea pig No. 8. The specific lesions were reproduced in this animal and the specific organism recovered from these lesions. The lesions were again reproduced in guinea pigs No. 13 (with the stomach contents of No. 8), 14 and 15 (with bacterial filtrate from No. 8).

Morphology and Cultural Characteristics. This organism varies considerably in morphology. The typical form (when stained by Gram's method) is that of fine slender rods with pointed or rounded ends from 0.1 microns to 0.4 microns in diameter by 0.5 microns to 3 microns in length. In the tissue the rods are so short that they resemble micrococci and comma-shaped bacilli, which are hardly visible. The various forms are often associated in the same culture. This organism is easily confused with a Gram-negative short-chain streptococcus at times.

Staining. The organism is Gram-negative and is stained by the ordinary anilin dyes, with the exception of a few whose staining power is faint. Therefore the morphology of the organism is not so easily established, owing to the varied actions of certain anilin

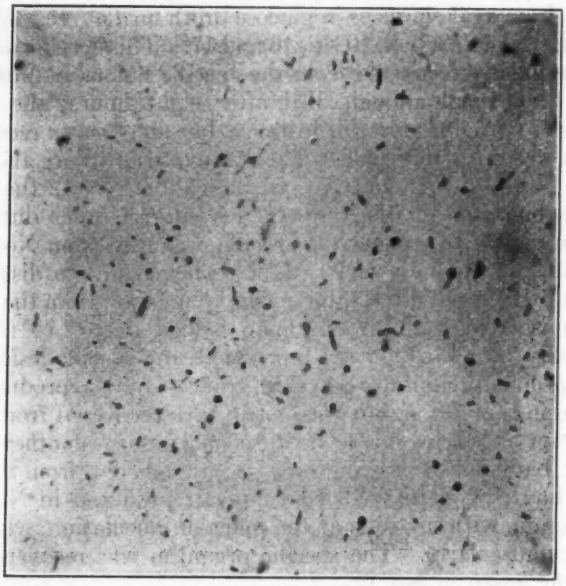

FIG. 5.—Specific organism, grown on nutrient agar for twenty-four hours and stained by Gram's method.

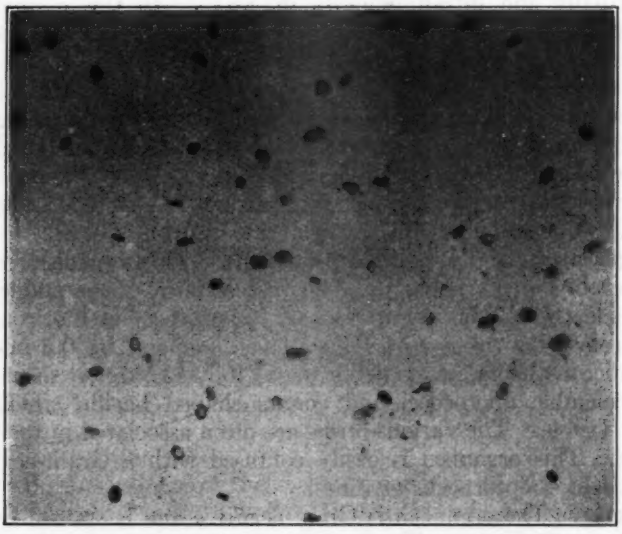

FIG. 6.—The same organism. Grown in glucose serum for six hours and stained by Bung's modification of Loeffler's method for flagella.

dyes, which on staining give the organism an entirely different aspect. When stained with Wright's stain it is faintly visible, resembling capsulated cocci. Under certain conditions the stained bacilli exhibit intracellular granules and bipolar bodies. They do not give the granulose reaction with iodin.

RESULTS OF EXPERIMENTS ON SEVENTEEN GUINEA PIGS.

Guinea pig No.	Weight before injection, gm.	Material injected.	Died.	Chloroformed.	Lived, days.	Necropsy.	Bacillus demonstrated.	Bacillus recovered.	Lesions reproduced.
1	480	Mr. H.; stomach contents; treated with 10 per cent sodium hydroxide; 5 cc suspect material, intraabdominally	×	0	17	Duodenitis and ulcer of stomach	×	×	×
2	500	Bacillus isolated from No. 1; 3 cc bacterial suspension, intraäbdominally	×	0	16	Duodenitis and ulcer of stomach	×	×	×
3	300	Bacillus isolated from No. 1; 1 cc bacterial suspension, intraäbdominally	0	×	6	Duodenitis and ulcer of stomach	×	×	×
4	200	Bacillus isolated from No. 1; ½ cc bacterial suspension, intraäbdominally	×	0	8 hrs.	Duodenum and stomach are hemorrhagic throughout	0	0*	×
5	515	Bacillus isolated from No. 3; 1 cc bacterial suspension, intraäbdominally.	0	×	30	Duodenitis	×	0*	×
6	445	Bacterial suspension (48 hrs. old), bacillus isolated from No. 3; 2 cc intramuscularly.	0	×	17	Myositis and duodenitis	×	×	×
7	450	Mr. N.; tonsils, extracts from (treated with 10 per cent sodium hydroxide); 3 cc intraäbdominally and intramuscularly	0	×	10	Myositis and duodenitis	×	×	×
8	780	Mr. L.; stomach contents; 2 cc intraäabdominally and intramuscularly	×	0	25	Duodenitis and ulcer of stomach	×	×	×
9	600	Bacillus isolated from No. 1; 2 cc intraäbdominally	0	×	25	Duodenitis	×	0*	×
10	525	Bacillus isolated from No. 1; 2 cc intraäbdominally	×	0	11	Duodenitis and ulcer of stomach	×	0*	×
11	400	Bacterial filtrate (48 hrs. old) from bacillus isolated from No. 1; 4 cc intraäbdominally	×	0	20	Duodenitis and ulcer of stomach	0	0	×
12	650	Bacillus isolated from No. 1; grown for 48 hrs. in glucose broth media; 4 cc intraabdominally	×	0	1	Hemorrhage in thorax	0	0*	0
13	675	Stomach contents from No. 8 guinea pig; 1½ cc intraabdominally	0	×	15	Duodenitis	×	×	×
14	240	Bacterial filtrate (48 hrs. old) from bacillus isolated from No. 8; ½ cc subcutaneously	0	×	19	Ulcers in duodenum and stomach	0	0	×
15	265	Bacterial filtrate (48 hrs. old) from bacillus isolated from No. 8; 1 cc intraäbdominally	0	×	19	Ulcers in duodenum and stomach	0	0	×
16	240	Bacterial culture (48-hr.-old broth culture) from bacillus isolated from No. 1; 1 cc intraäbdominally	×	0	6 hrs.	Hemorrhagic areas in duodenum and the stomach	0	0*	×
17	240	Bacterial culture (6-hr.-old broth culture) from bacillus isolated from No. 1; ½ cc intraäbdominally	×	0	20	Perforated stomach ulcer	0	0*	×

* No effort made to recover; see text.

Biology. It is an aërobic, nonmotile bacillus, and grows best at 30° to 37° C., and does not form spores. It grows readily on the usual culture media. The colonies upon agar are at first grayish-white, semitransparent, slightly raised and fimbriated. They have a very striking cultural characteristic (on agar), which is the complete disappearance of all the colonies after a certain period of incubation has elapsed, leaving in their places a highly refractive transparent film. Gelatin is liquefied, forming a crateriform stab at first. In glucose broth there appears a flocculent turbidity with subsequent formation of thin pellicles and grayish sediment. If the growth is left undisturbed in liquid media, pellicles will form. In inulin serum media there is a tendency to capsule formation. In saccharose, mannite, dextrose and neutral-red serum media the bacillus produces acid and does coagulate serum. Neutral red produces slight fluorescence. There is only a weak acid production in maltose, inulin and lactose. Russell's double-sugar media is acid in the butt and alkaline on the slant. Colonies grown on lead-acetate media are brownish-black in stab, while on the slant they are brown, with dark brown centers and crenated contours. The morphology varies in the different sugar media.

Pathogenicity. Guinea pigs inoculated with the specific organism, intraäbdominally or intramuscularly, showed lesions in the duodenum or stomach, or both, in which the bacillus was demonstrated (see table). Following this I had no difficulty in culturing the organism in such lesions or from points of inoculations. It has already been shown that with this recovered bacillus I was able to reproduce similar lesions in other guinea pigs.

If given small doses (0.5 to 1 cc) the animals survived from six hours to four weeks. On the other hand, 3 cc of a forty-eight hour culture killed a large guinea pig within twelve hours, with typical symptoms of toxemia starting with convulsions and leading to gradual paralysis and death. The regions involved were the duodenum and stomach, both showing striking inflammatory reactions and hemorrhagic areas. In the course of these subsequent experiments I was able partially to protect another pig by giving 2 cc of rabbit blood serum (the rabbit was partially immunized with the organism) after the onset of the first symptoms which occurred after one hour. The animal seemed to improve at first, but grew gradually worse, and six days later I observed profuse bleeding from the rectum. The animal was chloroformed. Necropsy revealed necrosis at the point of inoculation and slight myositis in the right hind leg, being the side on which injection was done. In the abdominal cavity there were no lesions of any kind. The duodenum, however, had six small, almost perforated, inflammatory ulcers surrounded by white rings. The stomach revealed one large ulcer, from which blood was still oozing. Another pig inoculated at the same time, but given an equal mixture of the serum (3 cc

and broth culture 3 cc., which stood for ten minutes before inoculation) remained in perfect health. The sterile broth filtrate (the organism had been grown in broth media for forty-eight hours) produced duodenitis and ulcers of the stomach after twenty days in the same manner as the organism itself. Secondary invaders, namely streptococci and other organisms, also could be readily demonstrated. My experiments indicate in the case of the specific organism that washings from agar slants are not very toxic to guinea pigs, though rabbits inoculated intravenously with dead cultures showed within a few hours grave symptoms of toxemia, which lasted for days without much improvement. Three cubic centimeters of broth culture (intraäbdominally) proved fatal within twelve hours to a rabbit weighing 8 pounds.

The intravenous injection of 2 cc of a suspension grown in Rosenow's[1] glucose brain media proved fatal within two hours to a rabbit weighing 7.5 pounds. There were hemorrhagic areas throughout the stomach and very marked lesions at the pylorus.

In view of these findings, I consider that ulcers of the duodenum and stomach may be due to a specific organism.

Conclusions. 1. From the experimental work in question, it would appear that there is a specific organism which exercises a selective affinity for the stomach and duodenum, and that it tends to produce ulcers in these localities.

2. Material taken from human beings diagnosed as suffering from gastric or duodenal ulcers, or both, when injected into guinea pigs, produced in the animals with great regularity either marked duodenitis or ulcers, or both. (In 2 cases in which the injection had been made intramuscularly there resulted duodenitis and myositis.)

3. From these lesions in the guinea pigs scrapings have been taken, the specific organism recovered therefrom, and on reinjection in pure culture in other guinea pigs it has produced similar lesions.

4. Mixed infections were sometimes found at the site of the ulcer, but the specific organism described was recovered (if it had been originally present in the material injected) every time the attempt at recovery was made.

5. Sterile filtrates of the specific organism (grown in the broth media for forty-eight hours) produced the same lesions as the organism itself.

NOTE.—These experiments were made possible through the courtesy and collaboration of the Clinic Staff of the Johnston-Wickett Clinic, Anaheim, California.

[1] Med. Clin. North America, Mayo Clinic, September, 1921.

THE SIGMOIDOSCOPIC PICTURE OF CHRONIC ULCERATIVE COLITIS (NON-SPECIFIC).

By Burrill B. Crohn, M.D.,

AND

Herman Rosenberg, M.D.,

NEW YORK.

(From the Medical Department, Mount Sinai Hospital, New York City.)

As time passes, we are becoming more and more familiar with the recognition of the course, pathology and the treatment of the malady which is identified under the name of idiopathic ulcerative colitis, simple ulcerative colitis, colitis gravis (Rosenheim), or chronic ulcerative colitis of the nonspecific variety. At this moment we are excluding from discussion the specific varieties of ulceration of the colon, such as amebic colitis, specific dysentery due to any one of the various types of bacillus dysenteriæ, diphtheritic colitis, or forms of chronic infection of the colon due to parasitic invasion. The discussion of the nonspecific form of ulcerative colitis restricts itself to those cases in which no recognized microörganism can be identified as the offending factor. It deals with a subacute or chronic disease characterized by a chronic inflammation of the mucous membrane and walls of the large intestine, in the pathologic picture of which ulceration predominate. The course is in most cases a chronic one, extending over months and years, not always or often a continuous one, but one that is punctuated by long periods of remission followed by severe and repeated recurrences of all of the symptoms. Fever, malaise, prostration, protracted and persistent diarrhea with some tenesmus and the passage of blood, mucus and pus, characterize the progress of the case. The course is usually rapidly downward; a loss of strength and weight is the rule, the loss of flesh extending up to 40 to 60 pounds in a period of a few months. An advanced secondary anemia occurs in severe cases, exceptions to which rule are few in number. The severity of the disease is well indicated by the name "colitis gravis," given to it by Rosenheim, indicating that chronic invalidism or death is a greater probability than recovery. By the same token the unsatisfactory status of the previous methods of therapy is most clearly indicated.

In the current literature the factors of etiology, symptomatology, the clinical course and prognosis have been ably described and summarized. Most thorough descriptions of simple ulcerative colitis have been published by Albu, Schmidt, Yeoman, Logan, and quite recently by Lynch and Felsen. These papers have covered series of cases which for this disease, in the experience of any one

person, have been fairly large, Logan's publication in 1919 revealing the unusually extensive collection of 117 cases. To the classic description of the disease given by these various authors we can add but little; we have devoted our attention to the field of therapy and the sigmoidoscopic picture of the healing colon.

During the years 1921 to 1923 inclusive we have observed at the Mount Sinai Hospital a series of 29 cases. Careful sigmoidoscopic examinations have been made in all instances, not only as an indispensable means of establishing a diagnosis or of observing the pathologic picture, but repeated sigmoidoscopies have been liberally used to check up the results of our various therapeutic endeavors.

NOTE.—A short word of warning should be issued on the possible dangers of the use of the sigmoidoscope. In even the most experienced hands a rupture of the rectum or sigmoid is possible. It has happened to even the most able men. The instrument must be introduced slowly and *under control of the eye.* Undue force exerted at any point is to be avoided. In instruments in which an air bulb is used as an inflating device the avoidance of too much pressure within the rectum is absolutely essential. A rupture of the intestine, of the sigmoid or of the rectum must be followed by an immediate laparotomy with suture of the rent. If this be done little evil consequence can follow. If time is lost or any other method is attempted to cover over or hide the accident a fatality will probably, if not surely, ensue.

The Pathologic Picture. The process of ulceration and inflammation that characterizes the disease is one which may involve the whole or some of the segments of the large intestine. In the milder cases only the rectum, or the sigmoid, or both may be involved. In the severer cases, particularly those of long standing, the entire colon from rectum to cecum, and even a small stretch of the terminal ileum may be the seat of the disease. It has been claimed that the disease may affect only segmental areas of the large intestine, such as the descending colon or the cecum. If so, we have not observed such cases, for in all the instances in which the disease has led to death, the autopsy has revealed almost universal ulceration of the entire large intestine, from anus to cecum and even to ileum. These cases, of course, have evidently been examples of the most severe and fatal form of the disease. In 1 case in which cecostomy was performed the laparotomy revealed a gut which was so indurated with inflammatory exudate that the entire colon felt like a rigid tube, all pliability having disappeared. Upon lifting the sigmoid the entire descending colon rose with it; the same applied to the ascending colon on the right side. On the other hand, in the milder cases, particularly those that run a subacute course, the pathologic process seemed restricted to the rectum and pelvic colon, since in passing the sigmoidoscope upward it was

seen that the brunt of the force of the disease was expended on the lower rectum, particularly that section of the ampulla of the rectum which directly adjoined the internal sphincter. The valves of Houston come in for a large share of the injury, the lower fold particularly being commonly the seat of the largest and most extensive ulcerations.

In one of our cases the colitis was observed to follow the spontaneous rupture of a rectovaginal abscess, the latter occurring as a sequel to a streptococcus tonsillitis, with erythema nodosum and a purpuric rash as concomitant symptoms. The rectovaginal abscess ruptured into both cavities, leaving a permanently communicating fistula. The ulcerative colitis followed shortly and has remained for several years, being lighted up from time to time by fresh attacks of tonsillitis and erythema nodosum. Other cases have followed both internal and external hemorrhoids, probably with secondary infection. It would thus seem that not only is the rectum the most frequent portal of entry for the infection, but that the initial pathological lesion is resident in the rectal ampulla and anal canal, spreading from there upward as far as the sigmoid in the milder cases, and depending upon the duration and severity of the process as far as the transverse or ascending colon or cecum in the graver cases. This point is of importance not only because it bears upon the etiology of the disease but insofar as it furnishes the rational basis for the treatment by means of rectal irrigations applied from below upward. It again explains why in those cases which come earliest for treatment the best results are obtained by antiseptic nonirritant lavages, for the disease is still limited in the early stages to the lower segments and is thus within reach and amenable to our therapeutic efforts.

The Sigmoidoscopic Picture. The instrumental observations which we have made of ulcerative colitis are similar in all respects to the careful descriptions furnished in the recent publications of Yeoman and of Lynch and Felsen. We may, however, classify the various stages of the disease as observed through the sigmoidoscope into: (1) Acute or subacute stage; (2) the active chronic stage in which the disease is six months to two years or more in duration; (3) the later chronic nonhealing ulcerative stage; (4) the terminal picture characterized by polyposis of the colon or colitis polyposis cystica (Virchow). As late sequelæ, one may infrequently observe fibrous stricture of the rectum, and in one instance malignant degeneration of the polypoid state into frank carcinoma of the rectal ampulla.

These various stages may be observed by careful studies of the sigmoidoscopic picture at intervals of the disease. Even the earliest stages of polypoid formation may clearly be seen through the sigmoidoscope when one is acquainted with the pathologic process. In addition, one may observe the stages of regression

of the process, under successful therapeutic onslaughts; the disappearance of the superficial ulcerations in the subacute cases and the subsidence of the granular and ulcerative forms in the more chronic types.

The Acute or Subacute Stage. The sigmoidoscopic pictures of the early phases of the disease are characterized by the appearance of marked hyperemic congestion of the mucous membrane; the mucosa is in a stage of active inflammation, red, often fiery red, the venules dilated, the whole mucosa friable and bleeding wherever the instrument impinges upon the wall of the gut. Superficial ulcers varying from pin-head size to those larger ones 1 or 2 cm. in diameter dot the entire visible mucosal area. The hemorrhage from even these small ulcers may be so excessive as to resemble blood squeezed from a sponge. Here and there a deeper punched-out ulcer is seen, usually occupying the lower reaches of the rectal ampulla and most commonly situated on one of three folds of Houston, the lower fold being the most frequently involved. The number of ulcerations may vary from a few or up to hundreds. At times older and larger ulcers are situated at the rectosigmoid angle or in the lower portions of the pelvic colon.

The whole mucosa is covered by a mucoid exudate, which in the later stages become purulent. In cases of unusual severity one may note large areas covered by a fibrinous or fibrinopurulent membrane, which resembles the pseudomembranous deposit of a severe pharyngitis or of a diphtheritic tonsillitis. This membrane is more or less strongly adherent; at other times it is easily frayed by the passage of the instrument over it, leaving an eroded bleeding surface.

In 1 case of a fulminating type, with a temperature of 104° F. and extreme prostration with almost incessant diarrhea, the picture was described as consisting of deep jagged irregular ulcers, bleeding freely and extending from the internal sphincter as far up as the instrument would reach (30 cm.). The ulcers could be easily palpated through the anus, covering the lower fold of Houston on the lateral walls of the rectum. The whole makes the impression as of "raw beef," the superficial mucosa having been entirely exfoliated, leaving the raw tissues of the deeper layers exposed. Ruge, in 1907, described 75 cases which he termed purulent and ulcerative proctitis. In this series he emphasized the type of cases in which purulent inflammation rather than ulcers predominated. He considered the disease as one of proctitis rather than of colitis, a conception which is probably not correct, but one which rightly stresses the point that the origin and center of the pathologic process resides in the rectum and lower colon.

The Active Chronic Stage. This refers to those cases in which the disease has been actively present, giving clinical symptoms for from six months to two years. This picture is similar in many respects

to the above, but represents a less acute stage of the disease with a more advanced and progressive lesion. The severe acute inflammatory congestion is less marked. On the other hand, ulcers are more numerous, are deeper, more irregular and extensive in diameter and appearance. The walls of the ulcer are less undermined and more discrete than is seen in amebic colitis. It is only in the severer and in the fatal cases, such as come to autopsy, that one sees the entire mucosa replaced with sinuous or transversely linear ulcerations that merge the one into the other and that burrow under the mucosa until the entire submucosa is exposed. One sees in this chronic and active stage of the disease the picture of severe ulceration; between the ulcers the mucosa is heaped up and hypertrophic, friable, sanguinous. The whole lumen of the gut is often filled with fresh red or older black (clotted) blood. The discharge from the surface consists of thick glairy mucus or of mucopus; at times a free purulent exudate is discharged from the anus, causing an irritative perianal dermatitis. Not infrequently suppurative condylomata appear around the margin of the anal ring, these consisting of raised papilloma-like acuminate outgrowths. External hemorrhoids are practically never absent and are a logical sequel to the constant pressing and straining incident to ten to twenty stools per day.

The Late Hypertrophic or Granular Stage of the Disease. This phase is seen as a later stage of the above process, a stage in which the active inflammatory period is accompanied by a granulating less active, more indolent reaction. It may last for many years and may be present during the periodic exacerbations of the course that characterizes the prolonged clinical picture.

The sigmoidoscopic picture of this stage is characterized by a persistence of ulcerations, some of them small and scattered, others again numerous, larger, irregular, deep and heaped up indurated inflammatory borders. This picture is to be recognized by the fact that the stage of intensive ulceration in the depths is replaced by one of a proliferative hypertrophic and granulating reaction. The ulcer walls themselves are more raised and thickened than deep. The mucosa between the ulcers is thrown up into hypertrophic villous-like folds. Multiple ulcers in the submucosa may be seen separated by bridges of hypertrophied mucosa which in many places are so thickened that they resemble polyps with sessile bases. In other areas more free from ulcers, or in places where superficial ulcerations have undergone retrogression, the mucosa may appear less congested, grayish-pink in color, the surface being granular and uneven, giving the appearance as if dotted with swollen tapiocal granules. This is the stage of chronic granular or follicular colitis and represents a later and less active or indolent stage of long standing inflammation. It may also be present and persist to a degree during those months or years in

which the disease passes into an intermission period with general freedom from active symptoms but with a persistence of 1, 2 or 3 semisolid stools passed with some urgency, usually in the morning. As such it may assume the type of matutinal diarrhea, or again of orthostatic diarrhea (diarrhea on assuming the erect position). The patient at this period may think himself apparently well; he is at least comparatively free from symptoms, may resume his, or more frequently her, occupation, and may retain his weight or even recover some of the excessive loss of flesh that is incidental to the more active stage of the disease. The granular colitis may be present as the sole remnant of a previous ulcerative stage or may be part of the picture only of a more severe hypertrophic reaction. Coincidentally areas may be seen, where the mucosa is pale and smooth and somewhat shiny, with newly formed arterioles visible, traversing the healed or healing areas of mucosal tissue. In the late stages, particularly where spontaneous healing is taking place and the clinical phenomena are all subsiding, the only sigmoidoscopic picture may be one of a dry glazed mucosa, granular and uneven in appearance, covered by strains of glairy mucus. Ulcers are no longer visible.

Polypoid Colitis. When the disease extends more or less actively over many years, showing little or no tendency to spontaneous healing, one may observe a final stage, a stage which is characterized by the great predominance of the hypertrophic or regenerative element running hand-in-hand with the persistence of indolent or partially healed ulcerations. Cases of colitis, or of chronic "dysentery" with polypoid excrescences had been described in the literature as early as 1721 by Menzel and in 1832 by Wagner. Rokitansky described the mechanism by which such proliferative processes are formed. He attributed the origin of the small excrescences seen in cases of healed or healing colitis to small islands of persisting mucous membrane that remained after the ulcerative process had ceased. The polyps formed on the edge of ragged margins of healing ulcers. Virchow elaborated the description of this polypoid degeneration of the inflamed mucosa in cases of colitis; he described the polyps as being vesicular fluctuating prominences scattered over the surface of the mucosa. The surface of these polyps was often depressed; from them could be expressed gelatinous mucoid material which apparently had accumulated in the dilated crypts of Lieberkuhn which composed the stalk and body of those newly formed excrescences.

One may add to this description the contribution of Hewitt and Howard who advanced the idea that since at least in the upper colon the polyps seemed to be situated at the line of the entry of the blood supply, namely, the mesenteric attachment, that therefore the polyps arose from areas of tissue which because of their better vascularization had withstood the ravages of the destructive

ulcerative process. The resultant increased blood supply to these surviving shreds of tissue resulted in active hyperplasia of the mucous glands and submucous connective tissue with consequent polyp-like formation. A secondary contraction of the proliferated fibrous tissue resulted in occlusion of the tubules at their bases and retention of the mucous contents to form a cyst. As the tissue at the base contracted, the proliferated hyperplastic tissue stood out more and more until a well-defined polyp appeared over the surface of the mucosa.

Thus the stage of polypoid colitis may take place as part of the picture of an old chronic colitis of long standing but with healing tendencies. The initial stage of polypoid colitis was seen by us through the sigmoidoscope in 1 of our cases, all the different elements in the process being readily distinguishable. Or the polypoid appearance may be the sole remnant of a healed colitis in which the ulcers have disappeared and the healing of the mucous erosions advanced to a terminal stage.

As final complements of long standing ulcerative colitis, we have observed in 2 cases well defined stricture formation of the lower reaches of the rectal ampulla. The area about the lower valve of Houston, and particularly between that fold and the internal anal sphincter seems to bear the brunt of the disease, since it is to this point that the irritating mucopurulent secretions are swept. Gravity alone would cause the collection of such fluid or semifluid material to collect in this area. The result is deeper ulcers at this location, ulcers that penetrate through the submucosa and probably involve the powerful underlying muscular bundles of the levator ani and similar constrictor muscles. As these ulcerations tend eventually to heal there is a constant tendency to scar and stricture formation, the end result of which is readily distinguishable with the palpating finger. The thickened lowermost valve of Houston often forms the base of the obtruding scar-tissue diaphragm.

Such a stricture-forming process may be felt even in an earlier stage in many cases of ulcerative colitis; it is quite characteristic of this particular pathological process.

Finally, we have observed in 1 case a malignant degeneration of the late stage of a polypoid ulcerative colitis, with the frank occurrence of a carcinoma of the rectal wall. In brief, this was a case of a nonspecific ulcerative lesion of the colon, fourteen years or more in duration. Many years previously a cecostomy had been performed for the relief of symptoms. The relief afforded was disappointing, the symptoms continuing on and off with practically no intermission during the entire period. The polypoid stage of the disease was already in evidence ten years ago. More recently the patient again came under observation with renewed symptoms of his disease. The sigmoidoscopic examination revealed an

extensive polypoid colitis, in addition to which one observed on the left lateral wall of the rectal ampulla, growing in a mass of polyp-like excrescences, an ulcerating massive neoplasm. Sections removed for histologic examination showed the presence of adenocarcinoma.

The value of this observation lies in the fact that the individual was under the observation of one of us for various periods during the entire course of the disease, all the stages being more or less observed during the frequent admissions of the patient to the wards of Mount Sinai Hospital. It is obvious that the carcinoma of the rectum might have occurred as an incident without relation to the presence or absence of such a chronic inflammatory lesion. But it is more natural as well as logical to connect the two facts and attribute the occurrence of an adenocarcinoma of the rectum to a malignant degeneration of a polypoid colitis under conditions of continued and long standing inflammatory traumatic insult.

Multiple polyposis of the colon as a primary condition independent of ulcerative colitis has been extensively described by Doering and recognized by Lockhart-Mummery. He collected from the literature 50 cases in 24 of which (46 per cent) malignant carcinomatous degeneration had taken place. The great tendency to cancerous development on such a basis is a conceded fact. It is, therefore, not surprising that a similar malignant change should have been observed in the terminal polypoid stage of ulcerative colitis.

Summary. The pathologic areas involved in cases of non-specific ulcerative colitis may be distributed throughout the course of the colon, or in patches.

According to the sigmoidoscopic picture one recognizes progressive stages such as:

1. Acute or subacute stage.
2. Active chronic stage.
3. A later granular ulcerative stage.
4. Terminal picture of colitis polyposis cystica (Virchow).
5. As sequelæ one may occasionally see mild stricture formation or a carcinomatous degeneration of the polypoid state.

The stage of healing may be extremely rapid, so that the regressive or reparative process may change an ulcerative hemorrhagic area into a healed mucous membrane within a few weeks.

REFERENCES.

Rosenheim: Deutsch. Med. Wchnschr., 1908, **38**, 265.
Albu: Mitt. a. d. Grenzgeb., 1914, **28**, 386.
Yeomans: Jour. Am. Med. Assn., 1921, **77**, 2043.
Schmidt, Ad.: Schmidt. u. Noorden-Klinik der Darmkrankh., 2d ed., 1921, p. 487.
Logan: Northwest Med., 1919, **18**, 1.
Lynch and Felsen: Non-specific Ulcer, Colitis Monograph, 1923
Ruge: Arch. klin. Chir., 1907, **80**, 3.
Menzel (quoted by Hewitt and Howard): Arch. Int. Med., 1915, **15**, 714.

Wagner (quoted by Hewitt and Howard): Med. Jahrb. d. k. k. Ost-Staates, 1832, **11**, 274.
Rokitansky: Lehrbuch der pathogischen Anatomie, 3d ed (revised, Wien, 1861, **3**, 209).
Hewitt and Howard: Arch. Int. Med., 1915, **15**, 714.
Doering: Arch. klin. Chir., 1907, **83**, 194.
Lockhart-Mummery: Diseases of Rectum and Colon, London, 1923.
Virchow: Die krankhaften Geschwulsten, Berlin, 1863, **1**, 243.
Woodward: Am. Jour. Med. Sci., 1881, **81**, 142.
Flexner and Sweet: Jour. Exper. Med., 1902, **6**, 181.

THE POSSIBLE RELATIONSHIP BETWEEN GUANIDIN AND HIGH BLOOD PRESSURE.*

By Ralph H. Major, M.D.,
KANSAS CITY, KANSAS.

(From the Department of Internal Medicine, University of Kansas School of Medicine Kansas City.)

The thought that arterial hypertension is produced by some undiscovered or unstudied product of metabolism has often been expressed. Some writers have suggested that the overproduction of some substance may be responsible for the production of high blood pressure, while others, with the picture of chronic nephritis and its impaired excretion in mind, have thought of the retention of some substance as the causative factor in arterial hypertension.

As a contribution to this subject we began about eighteen months ago a systematic study of the pressor effects of various substances present in the normal urine. One of the substances studied, methyl guanidin, has such powerful and prolonged pressor effects as to suggest that it may be at least one of the metabolites concerned in the production of high blood pressure.

Methyl guanidin was first demonstrated in the urine of normal persons by Kutcher and Lohmann, in 1908, and has been subsequently studied, particularly by Noël Paton and his co-workers, who assert that it is the toxic substance responsible for the production of tetany.

In our experiments we have used methyl guanidin sulphate, methyl guanidin nitrate and also dimethyl guanidin sulphate, guanidin carbonate, guanidin thiocyanate and guanidin hydrochlorid. All of these guanidin compounds show a very striking ability to raise the blood pressure and to maintain it at a high level. Following the intravenous injection of 0.1 gm. to 0.2 gm. of methyl guanidin sulphate per kilo of body weight the blood pressure in dogs is often doubled or even tripled, this high pressure persisting often

* Read before the Annual Meeting of the Association of American Physicians, Washington, D. C., May 5, 1925.

from four to five hours. Similar results have been obtained following intramuscular injection and from administration through a stomach tube. Larger doses usually produce a fall in blood pressure, accompanied by paralysis of respiration, irregular heart action and twitching or convulsions similar to those observed in tetany.

We have also studied some of the features of the mechanism by which this high blood pressure is produced. Section of the vagi, after injection of the guanidin compounds, has no effect on the high blood pressure, and if both vagi are cut before injection the blood pressure rises just as in normal animals. In the decerebrated dog, whose medulla is destroyed, injection of methyl guanidin still produces an elevation in blood pressure. We have also noted a marked blanching of the ears of rabbits following injection, and in studying the retinal arteries with the ophthalmoscope we have actually seen a constriction of the arterioles following injection of guanidin compounds. These observations suggest that a peripheral constriction of the arterioles is responsible for the elevation in blood pressure, an experimental observation in harmony with much of the best thought on the mechanism of the production of hypertension in man.

The next phase of our work was to study the urinary secretion of the guanidin bases in normal individuals, in dogs with experimental uranium nephritis and in patients suffering from chronic nephritis and essential hypertension. The most satisfactory method we have used has been that of Findlay and Sharpe, the principle of which is the removal of proteins by tannic acid and the precipitation of the guanidin bases with picric acid in the form of dimethyl guanidin picrate. This method does not change creatin or creatinin into guanidin, which apparently happens in some of the other methods where mercury salts are used.

A study of the urinary excretion of the guanidin bases in normal individuals has shown considerable daily variations, as is the case with some of the other nitrogenous substances, but most normal individuals have shown an average of 100 mg. per day. In experimental uranium nephritis, and in chronic nephritis with hypertension, the daily excretion of the guanidin bases has uniformly shown a decrease when compared with normal individuals, the curve of guanidin excretion following roughly the curve of nonprotein nitrogen excretion. In essential hypertension we have usually found a diminished excretion of guanidin, although this has not been constant.

We have recently studied the excretion of guanidins in 2 patients with essential hypertension, admitted to the hospital with marked myocardial insufficiency, edema and poor urinary excretion. The patients were treated with digitalis and diuretin, the blood pressure fell markedly, the urinary secretion was markedly increased and there was a very marked increase in the excretion of guanidin

bases. These observations suggest a retention of the guanidin bases during the period while the blood pressure was so high.

The methods that have been used for the determination of the blood guanidins up to the present time have been so time-consuming, and have required such large amounts of blood for the determinations, that they have not found much clinical application. The colorimetric method devised by Marston represents an important step toward the solution of this problem.

The addition of Marston's reagent to an aqueous solution of guanidins produces an intense red color which can be used for a colorimetric determination. Pure creatin or creatinin gives no reaction and urea shows no color until a concentration of 500 mg. per 100 cc or greater is reached. The addition of this reagent to blood serum, diluted with distilled water, or to an aqueous extract of certain tissues gives a red color which is increased when guanidin compounds in very small quantities are added. Marston has pointed out that ammonia and uric acid may interfere with the reaction if their concentration is high and the amount of guanidin very small.

We have examined the blood serum of a large number of normal individuals and of patients suffering from arterial hypertension, but have found no increase in guanidin in the blood of patients with high blood pressure. This has led us to a further study of the blood guanidins of dogs after the injection of guanidin compounds, and we found that while the guanidin content of the blood is increased for two or three minutes after injection, this excess has largely or entirely disappeared in five minutes, although the blood pressure continues elevated for four or five hours.

Such findings suggest certain possibilities: Rapid excretion of guanidins, storage in some tissue, transformation into some other substance which has a prolonged pressor effect, or rapid saturation with destruction of the excess.

The urine after injection of guanidin compounds shows, however, no constant increase in guanidin bases, and removal of both kidneys, excluding the possibility of urinary secretion does not prevent the rapid disappearance of guanidin from the circulation. The guanidin content of the muscles, lungs, liver, heart, brain, spleen and kidneys after injection with guanidin bases is apparently no greater than that of normal controls. When we consider the possibility of guanidin being changed into some other pressor substance, a study of its chemistry would indicate that it is probably either transformed directly into urea or first into cyanamid and then into urea. We have studied the action of both urea and cyanamid and neither has any pressor effect.

These observations have led us to the view that the pressor effect of the guanidin compounds is apparently exerted almost immediately on the neuromuscular apparatus of the smaller bloodvessels. It is

probable that these tissues fix a certain amount of guanidin and the excess is very rapidly destroyed.

In addition to the study of the pressor action of guanidin, we have studied the effect of certain substances on the hypertension produced by guanidin. Veratrum viride and amyl nitrite produce only very transient effects upon this high blood pressure. Calcium chlorid, on the other hand, produces a permanent fall in blood pressure accompanied, however, by marked cardiac irregularity. When an equal quantity of potassium chlorid is added to the calcium chlorid a prompt fall in blood pressure without cardiac irregularity results, this fall being produced by either intravenous or intramuscular injections. If calcium chlorid and potassium chlorid are injected before guanidin compounds no rise in blood pressure occurs. This indicates a chemical action of these substances, neither of them having any marked effect upon normal blood pressure when injected in doses as large as those which will reduce the high blood pressure following the injection of guanidin. We have also produced a similar fall in blood pressure by the use of normal hydrochloric acid and ammonium chlorid.

Some very interesting results were obtained with the parathyroid extract of Hanson and of Collip. Both of these extracts reduce very promptly the hypertension produced by injection of guanidin compounds. It has also been noted that the blood calcium, following injection of the guanidin compounds, fell and then rose following injection of the parathyroid extract. While the blood calcium was low the blood pressure was high, and as the blood calcium rose the blood pressure fell. We also found that certain other organ extracts, particularly that of the liver, lowered the blood pressure which had been elevated by guanidin compounds.

Summary. These observations suggest there may be a relationship between guanidin and arterial hypertension. The question is left unanswered as to whether high blood pressure is caused by an increased production of guanidins due to an error of metabolism, or due to a faulty excretion of guanidins by a damaged kidney. Our observations indicate that any great excess of guanidin is destroyed, although a part of this excess may be retained, probably fixed by the neuromuscular apparatus of the smaller bloodvessels with the production of an arterial hypertension.

BIBLIOGRAPHY.

1. Achelis, W.: Ueber das Vorkommen von Methylguanidin im Harn, Ztschr. f. physiol. Chem., 1906, **50**, 10.

2. Collip, J. B.: The Extraction of a Parathyroid Hormone which will Prevent or Control Parathyroid Tetany and which Regulates the Level of Blood Calcium, Jour. Biol. Chem., 1925, **63**, 395.

3. Engeland, R.: Ueber den Nachweis organischer Basen im Harn, Ztschr. f. physiol. Chem., 1908, **75**, 49.

4. Findlay, Leonard, and Sharp, J. S.: Adult Tetany and Methylguanidin, Quart. Jour. Med., 1920, **13**, 433.

5. György, P. and Vollmer, H.: Beeinflussung der Guanidinvergiftung durch Säurezufuhr, Arch. f. exper. Path. u. Pharmakol, 1922, **95**, 200.
6. Hanson, Adolph M.: The Hydrochloric X of the Bovine Parathyroid and its Phosphotungstic Acid Precipitate, Mil. Surgeon, 1924, **54**, 76.
7. Koch, W. F.: On the Occurrence of Methylguanidin in the Urine of Parathyroidectomized Animals, Jour. Biol. Chem., 1912, **12**, 313.
8. Kutscher and Lohmann: Der Nachweis toxischer Basen im Harn, Ztschr. f. physiol. Chem., 1908, **49**, 81.
9. Major, Ralph H. and Stephenson, Walter: The Effect of Methyl Guanidin on the Blood Pressure, Bull. Johns Hopkins Hosp., 1924, **35**, 140.
10. Major, Ralph H. and Stephenson, Walter: Further Observations on the Elevation in Blood Pressure Produced by Guanidin Compounds, Bull. Johns Hopkins Hosp., 1924, **35**, 186.
11. Major, Ralph H.: Relationship between Certain Products of Metabolism and Arterial Hypertension, Jour. Am. Med. Assn., 1924, **83**, 81.
12. Marston, Hedley R.: A Colorimetric Method for the Estimation of Guanidin and Methyl Guanidin, Australian Jour. Exper. Biol. and Med. Sci., 1924, **1**, 99.
13. Marston, Hedley R.: A Colorimetric Method for the Estimation of Guanidin and Methylguanidin. II. The Distinction between Guanidin and its Methyl Derivatives, Australian Jour. Exper. Biol. and Med. Sci., 1925, **2**, 57.
14. Nattrass, F. J. and Sharpe, J. S.: Adolescent Tetany and its Relation to Guanidin, Brit. Med. Jour., 1921, ii, 238.
15. Paton, D. Noël: Recent Investigations on Tetania Parathyreopriva and Idiopathic Tetany, and on the Functions of the Parathyreoids, Edinburgh Med. Jour. 1924, **31**, 541.
16. Paton, D. Noël and Findlay, Leonard: Tetania Parathyreopriva, Quart. Jour. Exper. Physiol., 1917, **10**, 315.
17. Watanabe, C. K.: Studies in the Metabolic Changes Induced by the Administration of Guanidin Bases, Jour. Biol. Chem., 1918, **36**, 531.

CALORIMETRIC STUDIES OF THE EXTREMITIES FOLLOWING LUMBAR SYMPATHETIC RAMISECTION AND GANGLIONECTOMY.*

By George E. Brown, M.D.,

and

Alfred W. Adson, M.D.,

Rochester, Minn.

(From the Division of Medicine, Mayo Clinic and the Mayo Foundation, and the Section on Neurologic Surgery, Mayo Clinic.)

The experimental and clinical work of Royle and Hunter on ramisection for spastic paralysis has awakened interest in the physiologic effects. The object of their experimentation was to confirm the work of Boeke, de Boer and Langelaän, with regard to the influence of the gray rami on the plastic tone of striated muscle. Being convinced that the gray rami play an important part in maintaining plastic tone, Royle applied the procedure, ramisection of the gray rami, to patients with spasticity and found that it diminished the plastic tone. He observed in 1 patient a change in temperature, the extremity operated on being warmer

* Presented for publication April 7, 1925.

to the touch than the one not operated on. Absence of sweating was also noted in the leg on the operated side in 1 patient. In view of this phenomenon, we believed it particularly important to study carefully the vasomotor effects on the extremities in cases in which ramisection had been done. We have attempted to carry out such studies in relation to skin temperature, heat production and radiation of the lower extremities before and after operation in 5 cases of spastic paraplegia.

Operative Procedure. Inasmuch as we decided to perform a bilateral lumbar ramisection, we employed a median-line incision extending from the symphysis to a point 7.5 cm. above the umbilicus. The patient was placed in the Trendelenburg position, and the intestines were displaced upward by a pack. The posterior wall of the peritoneum was incised on the right side along the margin of the inferior vena cava and the right common iliac vein. The dissection was then carried down to the mesial border of the psoas muscle, retracting the ureter outward and the inferior vena cava mesially, exposing the lumbar sympathetic trunk and ganglia with the gray rami, passing along with the intervertebral vessels to communicate with the spinal nerves at the intervertebral foramina.

Royle advocated only the division of the rami, but we have learned that it is possible also to remove the second, third and fourth lumbar sympathetic ganglia with the sympathetic trunk without any serious complications of the hypogastric plexus. This procedure was employed in the 4 cases reported. The technic for the left side is similar to that for the right, except that if the sigmoid is firmly fixed in the left iliac fossa it is necessary to mobilize it by opening the peritoneum laterally to the sigmoid attachment; after this it may be elevated and displaced mesially, again exposing the ureter, retracting it outward and elevating the lower portion of the abdominal aorta and the common iliac artery, thus exposing the sympathetic ganglia, trunk and rami, which may then be removed as on the right side, making sure to divide the sympathetic trunk above the second lumbar sympathetic ganglia and below the fourth lumbar sympathetic ganglia.

Postoperative Caloric Changes. In order to determine the possible effects of this operation on the vasomotor nerves, the following plan of study was carried out in part or in whole before, and for variable periods after, operation.

1. Skin temperature determinations were made by means of the Tycos self-recording temperature apparatus under controlled conditions of room temperature and position, with uniform observation periods.

2. Calorimetric studies were made of heat production in the feet by means of the Stewart-Kegerreis calorimeter,[1, 3] under carefully checked and controlled conditions with regard to rest, and constant

room temperature. The basis of calculations of heat transference is given in small calories, each minute for each square inch of surface area.

3. Clinical observations were made relative to the subjective symptoms of the patient, color of the skin, behavior of the sweat glands and blood pressure readings. The time relationship is shown in Tables I and II. There was considerable difficulty in attempting to control muscular movement in the period following operation. These estimations were made at the bedside and controlled as far as possible.

Case Reports. CASE I.—The skin temperature determinations were made on the inner side of the thighs, the outer portion of the middle part of the legs and the palmar surface of the feet. The readings before operation showed a decreasing temperature toward the periphery; the afternoon following operation sharp increases were noted in all three areas in the right leg, but the greatest proportional rise, 6.1° C., occurred in the right foot. The next day there was a similar rise on the dorsal surface of the left foot. On the ninth day after operation the temperature of the thigh had returned to the preoperative level, while it was still elevated in the feet. The temperature of the mouth remained normal during the entire postoperative period.

CASE II.—The preoperative skin temperatures were higher in the right foot than in the right thigh. On the afternoon of operation a rise of 1.4° C. occurred in the right leg and a greater rise in the left foot. On the fourth day the temperature levels remained unchanged in the right leg, whereas there was some decrease in the left. Temperatures of the mouth were normal during the period of convalescence.

CASE III.—Sharp rises in temperature were noted in this patient. There were slight differences in the temperature of the thigh and feet before operation. On the day following operation an increase of 2.7° in the right leg and of 2° in the left was noted, whereas increases of 6.4° and 4° were obtained in the right and the left foot, respectively.

CASE IV.—The day following operation a temperature increase of 7.5° was noted in the left foot, and 3.6° in the outer aspect of the left thigh. Nineteen days after operation increases of 5.1° in the left foot and 2.6° in the right thigh were obtained.

CASE V.—Temperature increases of 2.5° occurred in the right foot the day following operation, while no change was demonstrated in the outer area of the thigh. Fifteen days later the right foot showed an increase of 1.2°, as compared with the preoperative temperature. There was no further change in the temperature of the thighs.

TABLE I.—SKIN TEMPERATURE DETERMINATIONS BEFORE AND AFTER ABDOMINAL SYMPATHETIC RAMISECTION AND GANGLIONECTOMY.

Case.	Date.	Age and sex.	Diagnosis.	Temperature.										Remarks.
					Right.†				Left.†					
					Thigh.		Leg.	Foot.	Thigh.		Leg.	Foot.		
				Mouth*	Inner.	Outer.	Outer.	Palmar.	Inner.	Outer.	Outer.	Dorsal.	Palmar.	
1	1924													
	7/ 4	10	Spastic	....	35.5	....	32.6	31.6	35.5	....	....	....	....	Bilateral lumbar sympathetic ramisection and ganglionectomy, July 5.
	7/ 5	M.	paraplegia	99.0	38.1	....	35.5	37.7	36.1	....	....	....	....	
	7/ 6			98.6	....	....	....	....	38.3	37.0	36.6	36.6	....	
	7/ 9			98.6	35.7	....	34.5	36.2	35.1	....	34.2	36.9		
	7/11			98.4	34.8	....	35.5	37.2	37.2	....	....	36.1		
	7/14			98.0	35.3	....	33.3	35.0	34.4	....	33.5	35.0		
2	7/ 7	12	Spastic	98.4	33.8	....	33.7	34.7	35.0	....	34.8	....	34.8	Bilateral lumbar sympathetic ramisection and ganglionectomy, July 8.
	7/ 8	M.	paraplegia	99.0	36.1	....	35.1	36.4	35.0	....	37.1	....	38.4	
	7/10			99.2	36.4	....	36.4	37.4	36.1	....	35.3	....	36.6	
	7/12			98.6	36.1	....	35.7	37.2	36.0	....	34.0	....	36.6	
3	9/30	24	Cerebral	....	33.1	....	32.5	31.6	33.8	....	34.1	....	34.1	Bilateral lumbar sympathetic ramisection and ganglionectomy, October 2.
	10/ 3	F.	palsy	....	37.0	....	35.2	38.1	36.1	....	36.1	....	38.1	
4	1925													
	2/24	28	Spastic	....	....	32.3	32.2	26.6	....	32.5	32.4	....	29.4	Bilateral lumbar sympathetic ramisection and ganglionectomy, February 26.
	2/27	F.	paraplegia	....	....	....	....	....	....	36.1	35.5	....	36.9	
	3/17					32.7	30.2	34.9	....	35.1	33.1	....	34.5	
5	2/16	51	Spastic	....	....	34.8	33.1	33.8	....	36.1	34.6	....	33.5	Bilateral lumbar sympathetic ramisection and ganglionectomy, February 17.
	2/17	M.	paraplegia	....	....	35.5	36.5	36.3	....	....	....	....	....	
	2/19	....	....	....	....	....	....	....	....	35.3	35.1	....	35.3	
	2/23	....	....	....	....	33.5	33.5	34.1						
	3/ 2	....	....	....	....	33.5	33.6	35.1						
	3/ 4	....	....	....	....	35.2	35.0	35.0						
	3/ 6	....	....	....	....	....	....	....	....	34.5	34.6	....	35.1	
	3/16	....	....	....	....	35.6	33.6	33.4	....	36.0	33.6	....	34.4	

* Fahrenheit. † Centigrade.

TABLE II.—CALORIMETRIC STUDIES BEFORE AND AFTER ABDOMINAL SYMPATHETIC RAMISECTION AND GANGLIONECTOMY.

Case.	Date, 1924.	Sex and age.	Diagnosis.	Blood Pressure.		Pulse.	Temperature.			Foot.	Total calories for twenty minutes.	Square inches of surface area of foot.	Calories each minute for each square inch.	Remarks.
				Systolic.	Diastolic.		Mouth.*	Outdoor.†	Room.†					
1	7/ 4	10	Spastic	106	50	80	97.4	20.0	23.0	Right	660	70	0.47	Patient at rest.
	7/ 4	M.	paraplegia	108	60	80	97.4	20.0	23.0	Left	1940	71	1.36	
	7/ 5	....	....	...	..	..	....	....	....	....	....	..	....	Bilateral lumbar sympathetic ramisection and ganglionectomy.
	7/23	....	....	98	58	96	98.8	30.0	29.5	Right	4600	..	3.28	Patient at rest.
	7/23	....	....	108	60	96	98.8	30.0	29.2	Left	3440	..	2.42	
3	9/30	24	Spastic	134	78	88	98.4	12.6	22.7	Right	600	73	0.41	Patient at rest.
	9/30	F.	paraplegia	134	78	88	98.4	12.4	22.1	Left	480	70	0.34	
	10/ 2	....	....	...	..	..	....	....	....	....	....	..	....	Bilateral lumbar sympathetic ramisection and ganglionectomy.
	10/30	....	....	125	75	84	98.0	25.2	24.3	Right	5600	..	3.83	After operation.
	10/30	....	....	125	75	84	98.0	25.3	25.7	Left	5500	..	3.92	Patient at rest.
4	2/24	28	Spastic	130	80	100	98.0	0.0	23.4	Right	560	69	0.40	Patient at rest.
	2/25	F.	paraplegia	128	80	85	97.8	9.3	18.2	Right	400	69	0.29	Patient at rest.
	3/19	....	....	...	..	..	....	....	....	....	....	..	....	Bilateral lumbar sympathetic ramisection and ganglionectomy.
	3/19	....	....	...	..	84	98.0	4.2	22.1	Right	1480	69	1.07	
	3/24	....	....	112	86	84	97.8	5.0	22.2	Right	1520	69	1.10	Patient at rest.
5	2/16	51	Spastic	130	80	80	98.0	0.0	22.8	Left	1840	77	1.19	Patient at rest.
		M.	paraplegia	...	..	..	....	....	....	....	....	..	....	Bilateral lumbar sympathetic ramisection and ganglionectomy.
	3/19	....	....	102	58	98	98.0	4.2	22.3	Left	4640	77	3.01	Patient at rest.

* Fahrenheit. † Centigrade.

Studies of the heat conduction from the feet made with the foot calorimeter† further confirm the existence of the increased flow of blood following lumbar sympathetic ramisection and ganglionectomy. Determinations of the normal heat radiation under controlled conditions from the feet have shown a range from 0.5 to 3 small calories each minute for each square inch of surface area. Higher values in normals have been found during periods of excessively hot weather and represent the physiologic effects for increased radiation of heat from the skin. In hospital cases with control rest periods before tests and with standard room tempera-

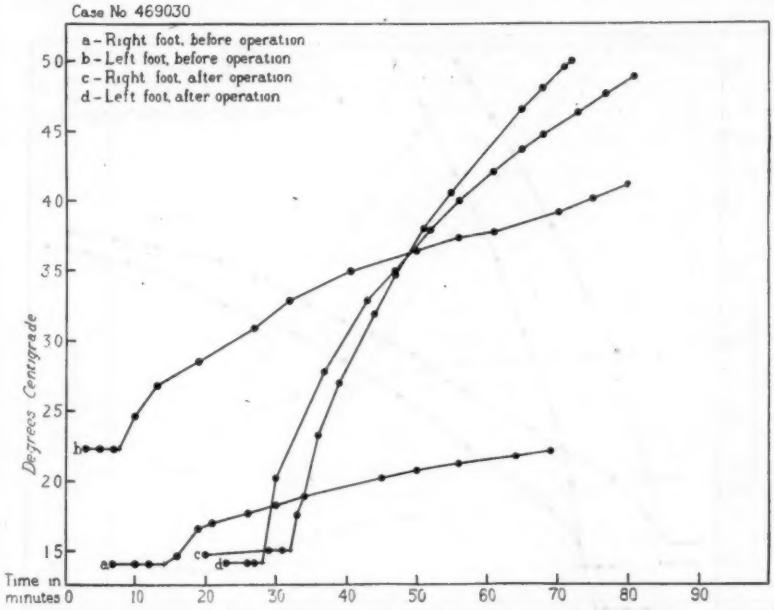

FIG. 1.—(Case I.) Heat curves, obtained by the Stewart-Kegerreis calorimeter, showing a marked increase in heat conduction from the feet, following lumbar sympathetic neurectomy.

ture a normal range of from 0.5 to 2 calories each minute for each square inch of surface area is found. Comparative readings under similar conditions check remarkably closely.

Preoperative values of 0.47 and 1.36 calories each minute for each square inch of surface area were noted in the right and the left foot, respectively (Fig. 1, Case I). Eighteen days after opera-

† This method determines the amount of heat given up to a known volume of water, in which the foot is placed. A special calorimeter is used. Corrections are made for heat loss of calorimeter and specific heat of metal container. A full report of the method, physical factors, and clinical studies is given in a group of papers by Sheard, Kegerreis and Brown.

tion the values were 3.28 and 2.42 calories. The total increase in calories amounted to 4000 and 1500 in the right and the left foot, respectively.

The preoperative values for heat production showed that the right foot in Case III gave up 600 calories in twenty minutes, or 0.41 calories each minute for each square inch of surface area, whereas the left foot gave up 480 calories, or 0.34 calories each minute for each square inch (Fig. 2). Twenty-eight days after operation the heat production had increased to 5600 and 5500 total calories for the right and left foot, respectively, or 3.83 and 3.92 calories each minute for each square inch of surface area.

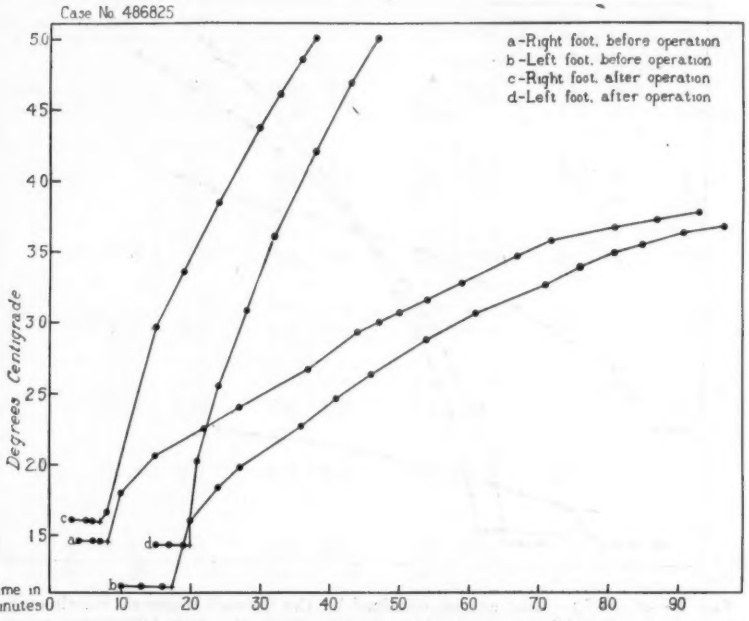

FIG. 2.—(Case III.) Increased heat production and heat conduction of the feet following lumbar sympathetic neurectomy, as determined by the foot calorimeter.

This change represents an increase of 900 per cent. These findings bore out the clinical observations, in which both objective and subjective findings attested to the hot dry condition of the skin.

Preoperative values for heat production in Case IV demonstrated that 0.29 and 0.4 calories were given up in the right foot each minute for each square inch of surface area. Thirty-two days after operation the heat production increased to 1.07 calories each minute for each square inch of surface area. There was a total increase of 1000 calories in the right and left feet following operation.

In Case V the preoperative values showed a heat production in the right foot of 1840 calories in twenty minutes, or 1.19 calories

each minute for each square inch of surface area. Thirty days after operation the total heat production had increased to 4640 calories during a twenty-minute period, or 3.01 calories each minute for each square inch of surface area. This represents an increase of 2800 calories, or 260 per cent.

Clinical Observations. The patient in Case IV was a young woman, aged twenty-eight years, who presented the clinical features of spastic paraplegia. Previous to operation the skin of the lower extremities showed a decreasing temperature toward the periphery. The feet were cool, pale and moderately moist. Following operation

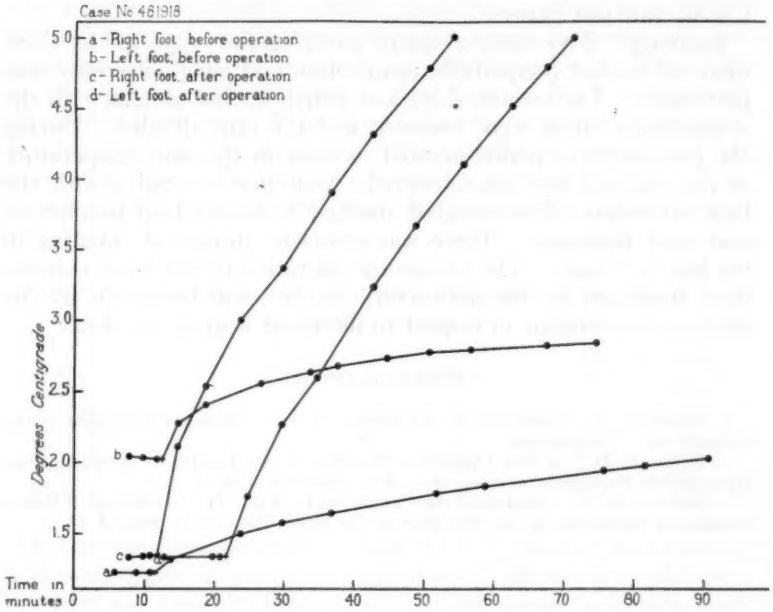

FIG. 3.—(Case IV.) Increased heat production and heat conduction of the feet following lumbar sympathetic neurectomy, as determined by the foot calorimeter.

and paralleling the calorimetric findings of elevated skin temperature the skin was very warm. A sharp temperature demarcation line could be established with the hand on the antero-lateral surface of the thigh 11 cm. below the anterior-superior spine. The feet were hot and dry. Twenty days after operation the feet were still hot to touch. There was no sweating below the line of demarcation. The skin of the dorsum of the feet had a slight ichthyotic appearance. Scaling was present. The lateral aspects of the feet were pink. The subjective symptoms were those of heat, although not to a degree to be troublesome. There were no demonstrable changes in the systemic blood pressure. A short, sharp attack of

cramps of the right quadriceps femoris muscles occurred forty days after operation.

In Case V the clinical manifestations of increased heat production were not as striking as in Case IV. The skin temperature of the feet was fairly high before operation; they were constantly warm and pink. Following operation no color changes were noted. Eighteen days after operation the skin was dry and scaly, especially of the palmar surfaces of the feet. The skin was hot to touch; the demarcation temperature line could not be established by touch. The subjective sensations were those of burning in the heels of both feet. No sweating could be demonstrated with Cobalt blue test papers.

Summary. Five cases of spastic paraplegia are reported in which bilateral lumbar sympathetic ramisection and ganglionectomy was performed. The second, third and fourth lumbar ganglia with the sympathetic trunk were removed and the rami divided. During the postoperative period marked increase in the skin temperature of the legs and feet was observed. Calorimetric studies with the foot calorimeter demonstrated marked increased heat production and heat radiation. There was complete absence of sweating in the legs in 2 cases. The vasomotor dilatation in the lower extremities, indicated by the calorimetric studies, was borne out by the clinical observations in respect to increased heat of the skin.

BIBLIOGRAPHY.

1. Sheard, C. S., Kegerreis, R. and Brown, G. E.: Calorimetric Studies of the Extremities. Unpublished.
2. Royle, N. D.: A New Operative Procedure in the Treatment of Spastic Paralysis and its Experimental Basis, Med. Jour. Australia, 1924, **1**, 77.
3. Stewart, G. N.: Studies on the Circulation in Man. II. The Effects of Reflex Vasomotor Excitation on the Bloodflow in the Hand, Heart, 1911–1912, **3**, 76.

DISEASE OF THE CORONARY ARTERIES.

Clinical and Pathological Features.

By M. H. Nathanson,
MINNEAPOLIS, MINN.

(From the Department of Medicine, University of Minnesota, Division A, General Hospital.)

An accurate conception of a disease depends on our ability to correlate clinical manifestations with pathological changes. It is unfortunate that various types of cardiac diseases are named and classified by the clinician without regard for the underlying structural changes found in the heart at necropsy. Myocarditis, for

example, is a frequent clinical diagnosis, yet pathologically, true inflammation of the heart muscle is an extreme rarity. Cases, so classified clinically, often present at autopsy an enlarged heart, with normal valves, normal coronary arteries and practically normal heart muscle on microscopical section. The same clinical term is applied to cases which show at postmortem advanced coronary disease and fibrosis in the myocardium.

From a study of clinical data and necropsy findings, it has seemed possible to identify certain clinical features with certain definite pathological conditions in the heart. This report consists of such an analysis in cases showing coronary disease at autopsy.

In postmortem records coronary sclerosis appears as a rather frequent cause of death in adults. The exact frequency of this condition is difficult to estimate. Of 849 autopsies in 1923, from the records of the Department of Pathology of the University of Minnesota, there were 28 deaths attributed to coronary sclerosis. Of these 849 cases 339 were above the age of forty years. Of the 28 coronary cases 27 were above this age (96.4 per cent). The following table gives the incidence in the various decades above forty years.

TABLE I.—INCIDENCE OF CORONARY DISEASE ABOVE THE AGE OF FORTY YEARS.

Age, years.	Autopsies.	Coronary disease.	
		No.	Per cent.
40 to 49	90	6	6.6
50 to 59	94	6	6.4
60 to 69	105	10	9.5
70 to 79	42	5	7.0
80 to 90	8	0	0.0

During the same age periods there were 70 cases of malignancy of various types as compared with the 27 of coronary disease. Twelve of the coronary cases were from the coroner's service, and this would have a tendency to exaggerate the frequency to a certain extent, since the incidence of coronary deaths in coroner's autopsies is greater than that of the average postmortem material. Although this would reduce the incidence of coronary disease in the general population below the figures given, this analysis indicates that the condition stands out as one of the frequent causes of death in individuals above the age of forty years. In spite of its relative frequency and serious nature, however, there appears to be no generally accepted clinical picture of this disease.

Coronary Sclerosis and Angina Pectoris. The clinical syndrome, angina pectoris, was first described as a disease entity by Heberden, in 1768. Following this Jenner and later Parry ascribed this condition to disease of the coronary arteries. Throughout the last century there was a general tendency to consider coronary sclerosis

and angina pectoris as synonymous. Even in the earlier literature, however, there are many reports of exceptions to the association of angina pectoris and coronary disease. The literature on this subject has been very extensive, and in more recent years a number of theories have been advanced for the causation of angina. Disease of the aorta, myocardial exhaustion and dilatation, neuritis of the cardiac nerves and many others have been suggested as the underlying mechanism of this disease. Huchard[1] collected as many as eighty hypotheses for the basis of angina. Allbutt[2] vigorously denies any relationship between angina and coronary sclerosis, and insists that the seat of the disease is in the proximal portion of the aorta. His views have attracted considerable attention, and have received support from other observers. It is not our purpose to discuss the various theories of angina. An excellent review may be found in Allbutt's book. It is sufficient to say, however, that careful observers have noted (1) coronary sclerosis at autopsy, without any of the clinical manifestations of angina, and (2) normal coronaries in typical cases of angina pectoris of long standing. It may be safely concluded then that the symptom complex, angina pectoris, cannot be accepted as the constant clinical expression of coronary disease.

Modern Clinical Concepts of Coronary Disease. In the textbooks and systems of medicine in common use there is little or no attempt to consider coronary sclerosis as a disease entity. As a result of the work of Herrick[3] in this country, the clinical manifestations of a sudden occlusion of a coronary branch have received considerable attention. Herrick has pointed out that death need not follow immediately on obstruction of a coronary artery. He has presented a clinical picture of this condition, and has described four types. Since Herrick first called attention to this disease, there have been a number of case reports of coronary thrombosis with fairly characteristic clinical pictures. As a result, coronary thrombosis holds a definite place as a disease entity in the majority of the more recent books in medicine. However, the clinical manifestations of the slower, progressive, obliterative changes in the coronary vessels have not been emphasized, and as a result there is a remarkable lack of uniformity in the manner in which this condition is considered in modern literature. With a few exceptions, there is no attempt made to discuss coronary sclerosis as an entity. Romberg[4] and Hirschfelder,[5] to be sure, devote portions of a chapter to a consideration of coronary sclerosis as a disease. Both emphasize cardiac pain and acute dyspnea as characteristic features. Paroxysms of rapid heart action are also described. Osler and McCrae[6] mention coronary changes in the discussion of angina, but report several cases in which the coronary arteries were negative. MacKenzie[7] makes no attempt to treat this pathological condition as a definite disease entity. He emphasizes the relation-

ship to angina, but coronary changes are also mentioned in a chapter on "The Senile Heart," which clinically presents different manifestations. In another publication, discussing heart pain,[8] he states that in hearts showing degenerative arterial changes at autopsy, "Pain was the chief symptom in a few, while others suffered no pain." Allbutt believes that sudden closure of a coronary artery produces symptoms, usually severe, sudden and protracted precordial or epigastric pain with collapse. He apparently, however, does not consider sclerosis, without sudden occlusion, of any great clinical significance, as the following statement from his book indicates: "It is freely admitted that coronary disease may, and indeed for the most part does, pursue its silent way without anginous or other storms." Lambert[9] does not believe that coronary sclerosis can be accepted as the anatomic basis of angina pectoris, and no attempt is made to discuss coronary disease as a clinical entity. Meakins[10] feels that we are not justified in accepting angina pectoris as a disease, but merely as a symptom complex for "a definite pathology of the heart muscle or coronary arteries has not been found." Thus, he treats neither angina nor coronary sclerosis as a disease, but in a chapter on cardiac pain merely refers to coronary sclerosis as a possible cause of this symptom. This brief review demonstrates that there is little attempt in the current textbooks to consider coronary disease as a clinical entity, and indicates the uncertainty and lack of uniformity in the present conception of the clinical significance of coronary sclerosis.

The object of this paper is to construct a clinical picture of coronary sclerosis from the analysis of the clinical data of a series of fatal cases which came to necropsy. The material for study was obtained from the Department of Pathology of the University of Minnesota and comprises records of 113 cases. All those included showed severe coronary disease, with marked narrowing and partial obliteration of one or more large arteries, and usually definite fibrosis or softening of the heart muscle. No case is selected in which there is not a marked narrowing of the lumen or a thrombus; and the general necropsy findings were such that coronary sclerosis was considered as a chief cause of death. It appears from the analysis of the available data that certain clinical manifestations are quite constant for the group as a whole. In other respects, however, there are definite differences in the picture presented. Thus a simple uniform clinical picture cannot be drawn, and subgroups, each with its own characteristic features, may be recognized. Thus the clinical data may best be presented in the following manner: (1) General clinical features, and (2) subgroups.

General Clinical Features. *Age and Sex.* The average age at the time of death was fifty-nine and two-fifth years. The youngest was thirty-two and the oldest eighty-eight years. There were but 2 cases under forty years and 73, or 65 per cent of the entire group

were between the ages of fifty and seventy years. The distribution in the various decades is shown in Table II. As to sex distribution, there was a definite preponderance of males. Of the 113 cases, 97 were males and 16 females, giving a ratio of 6 to 1. A correction is necessary, however, as in the necropsy material of the Department of Pathology there are at least twice as many males as females. This reduces the ratio to approximately 3 males to 1 female.

TABLE II.—AGE AT THE TIME OF DEATH OF 113 CASES OF CORONARY DISEASE.

Age, years.	No. of cases.
30 to 39	2
40 to 49	17
50 to 59	28
60 to 69	45
70 to 79	15
80 to 89	3

Symptomatology. The outstanding clinical feature, which was quite constant for the group as a whole, was the tendency for the symptoms to occur in attacks, unlike other forms of cardiac disease which usually develop with gradual onset and increasing intensity. Attacks were present in 80 per cent, while in 20 per cent the symptoms were those of progressive cardiac failure, and acute paroxysms were not prominent. As a rule, the attacks consisted of pain, less often of acute respiratory distress.

Pain. The type of pain was quite characteristic, being described most frequently as a sense of pressure or fulness rather than as an acute sharp pain. The following are some of the expressions commonly used, "an uncomfortable heavy feeling," "a sense of oppression or fulness," "a feeling of tightness or constriction," and in a few severe instances, "an intense vicelike sensation." Radiation to the shoulders and arms was quite infrequent, being present in but 10 per cent of the cases. In 3 instances the pain was limited to the left shoulder and arm. The most frequent site of the sensation of pressure or fulness was in the chest, being either substernal or precordial. However, in 25 per cent the pain was localized in the epigastrium. Belching, nausea and vomiting was frequently associated both with the chest and the epigastric types of discomfort. The descriptions often closely simulated the symptoms associated with various gastrointestinal disturbances, and in some instances resembled the picture which may be presented by an acute abdominal lesion. This condition undoubtedly explains some of the negative laparotomies, and the majority of deaths due to "acute indigestion," which are met with in those of advanced years.

Attacks of Respiratory Distress. This was present in about 10 per cent of the entire series. These attacks usually occurred in

cases in which the ordinary effort dyspnea of cardiac failure was absent or present in a minor degree. This symptom was most frequently described as a feeling of suffocation, or as a choking sensation, and often occurred during the night. The circumstances under which the attacks of pain and respiratory distress were induced are of interest. Although more frequently brought on by exertion, very often the attacks occurred during low levels of activity or awakened the patient from sleep. In one instance a diagnosis of an unimportant functional condition had been made, as the substernal distress was relieved by exercise. In a short time death occurred during an attack and necropsy revealed a marked coronary sclerosis. Sudden death likewise was usually not associated with exertion. The majority of deaths occurred during periods of rest or slight degrees of activity.

Although attacks were a constant feature of 80 per cent of the group, in 20 per cent the symptoms were those of progressive cardiac failure uninterrupted by attacks. Two characteristic features, however, were apparent: (1) Death occurred in most instances before edema of any degree had developed, and (2) sudden death terminated the cardiac failure with a greater frequency than occurs in failure associated with other types of cardiac pathology.

Clinical Types. The data presented thus far has dealt with the clinical manifestations which are fairly constant for the group as a whole. Coronary sclerosis presents a clinical picture which is quite uniform in certain respects. However, there is a definite lack of uniformity in two important features: (1) As regards the size of the heart, and (2) as regards evidences of congestive failure; thus subgroups may be recognized.

Size of Heart. In the majority of instances there was some increase in the weight of the heart, involving chiefly the left ventricle. The weight of the heart varied from 293 gm. to 850 gm., with an average weight of 464.2 gm. A heart weight of 400 gm. may be regarded as representing the upper limit of normal, and hearts weighing more than 400 gm., if valvular disease and glomerular nephritis are excluded, are usually indicative of hypertension. Of the 113 cases there were 68, or 60.1 per cent, in which the heart weight was above 400 gm., and 45, or 39.9 per cent, with a heart weight of 400 gm. or less. As regards the size of the heart, then, coronary sclerosis may be divided into two types: (1) With a heart of normal size; (2) with an enlarged heart, usually indicating hypertension.

Congestive Failure. When the heart fails stasis of the circulation occurs, resulting in certain symptoms and signs. The chief symptoms and signs are dyspnea, cough, edema and enlargement of the liver. Pathologically, the intensity of the passive hyperemia in the liver is the most accurate index of the degree of congestive failure. Judged by clinical signs and passive congestion of the

liver as found at postmortem, congestive failure was present in 46 cases, or 40.6 per cent, and absent in 67, or 59.3 per cent. Congestive failure was definitely more frequent in the cases showing cardiac enlargement. In the group with hearts of normal size congestive signs appeared in but 3 cases, or 6.6 per cent, while in 43, or 63.2 per cent, of those with enlarged hearts evidence of congestive failure was present. Taking into consideration, then, the variations in size of the heart and evidence of congestive failure, four subgroups may be recognized: (1) Heart of normal size, congestive symptoms absent; (2) heart of normal size, congestive symptoms present; (3) heart enlarged, congestive symptoms absent; (4) heart enlarged, congestive symptoms present.

Discussion. An analysis of the clinical and pathological findings in 113 fatal cases of coronary sclerosis which came to necropsy reveals the following. A fairly uniform clinical picture may be recognized, characterized by attacks usually of pain, less often of acute respiratory distress. In about 20 per cent, however, attacks do not play a prominent part, and the clinical manifestations are those of progressive cardiac failure. The 113 cases may be separated by the clinical and necropsy findings into four groups, because of the variations found in the size of the heart and evidences of congestive failure.

Type I includes those with a heart of normal size and without evidence of cardiac failure. The typical case gives a history of attacks of pain, either chest or abdominal, or of paroxysms of dyspnea. The patient otherwise seems in good health and there is no need for any limitation of his activities, as congestive failure is absent. Examination will show that the heart is not enlarged and usually no increase in blood pressure. This group presents considerable difficulty in diagnosis, as aside from the history of attacks, which may be very atypical, there are no symptoms or objective signs which indicate that there is either anatomical or functional damage to the heart. As a matter of fact, several cases had undergone a physical examination, and had been pronounced normal, and in a few instances an insurance examination had been successfully passed shortly before death. Of the 113 cases 37.2 per cent fall into this group.

In Type II are included those with hearts of normal size and with congestive symptoms present. This group exhibits a very different clinical picture, which is essentially that of cardiac decompensation. The patient is restricted in his activities because of shortness of breath on exertion, and edema may be present. Attacks of pain or acute respiratory distress may or may not be associated. There is little difficulty in recognizing that cardiac pathology is present, and coronary disease should be suspected as practically all other forms of cardiac pathology resulting in congestive failure are accompanied by enlargement of the heart, which is absent in this group.

Type III consists of those with cardiac enlargement in which the manifestations of congestive failure are absent. The picture is that of an individual who requires no restriction of activities and who is apparently in good health except for the occurrence of attacks of pain or acute respiratory distress. The heart is enlarged and the blood pressure is usually increased. This group is similar to Type I, but may be differentiated by the presence of cardiac enlargement and hypertension. This type includes 22.6 per cent of the entire series.

In Type IV are included the cases with cardiac enlargement and evidences of heart failure. The clinical picture is essentially that of cardiac decompensation. In most instances there is a history of attacks of pain or acute dyspnea, either preceding or associated with the symptoms of congestive failure, while in others attacks are entirely absent. Dyspnea and orthopnea are the outstanding symptoms. Edema is usually not marked or may be absent, and sudden death frequently terminates the cardiac failure. As to the recognition of this type, the evidence of reduction in functional capacity points at once to the heart as the seat of the pathology. As to the type of anatomical change, coronary sclerosis should be suspected when, in addition to the symptoms of congestive failure, there is also a history of attacks of pain or acute respiratory distress. Aside from the attacks, certain features are quite characteristic but not entirely diagnostic of this group. They are the following: (1) A history of congestive failure of comparatively short duration and rapidly progressive; (2) absence of marked edema; (3) tendency to sudden death; (4) a fairly characteristic electrocardiograph, with an abnormal form of the ventricular complex. Table III summarizes the essential features of the four types.

TABLE III.—CLINICAL TYPES OF CORONARY SCLEROSIS.

Clinical features.	No. of cases.
1. Heart not enlarged, congestive failure absent; symptoms of cardiac insufficiency absent; heart normal in size; blood pressure normal	42 or 37.2 per cent
2. Heart not enlarged, congestive failure present; symptoms of cardiac insufficiency present; heart normal in size; blood pressure normal	3 or 2.6 per cent
3. Cardiac enlargement, congestive failure absent; symptoms of cardiac insufficiency absent; heart enlarged; blood pressure increased	25 or 22.6 per cent
4. Cardiac enlargement, congestive failure present; symptoms of cardiac insufficiency present; heart enlarged; blood pressure usually increased	43 or 39.0 per cent

Illustrative Cases. TYPE I.—A male, aged fifty-four years, entered the hospital with the following history: He was in his usual health at the time of the onset of the present illness. While sitting in a chair he was seized with a severe pain in the abdomen. He fell

from the chair, and continued to complain of the pain. On examination the patient was practically comatose, there was a diffuse cyanosis of the skin, the heart was not enlarged and the tones were very weak. The systolic blood pressure was 50. There was tenderness in the upper abdomen and rigidity of the muscles. He was sent to the surgical division with a diagnosis of perforated gastric ulcer. On later examination the abdominal rigidity disappeared, but there was definite tenderness on pressure. The cyanosis increased and the patient died two and a half hours after admission.

At autopsy edema was absent. The heart weighed 325 gm. In the descending branch of the left coronary artery about 2 cm. from the opening there was a heavy calcareous intimal thickening, extending for a distance of about 2 cm. The lumen here was partially occluded. The entire length of this branch showed marked sclerosis. The other branches of the coronaries were slightly sclerotic but entirely patent. The root of the aorta was smooth. *The liver showed no evidence of congestion.* Other pathological findings were negative.

TYPE II.—A male, aged forty-six years, was admitted to the hospital with the following history. Five years ago he began to have attacks of precordial pain, and he also noted slight shortness of breath on exertion. Ten days ago he noticed swelling of the ankles, and his dyspnea became more marked. After four weeks' rest with improvement he was discharged from the hospital. He was readmitted two weeks later with similar complaints and his edema more intense. He was discharged from the hospital a month later, after some improvement. Nine days after discharge he was found dead in his room. A physical examination while in the hospital showed the following: Considerable edema; the heart was not enlarged and there was a blowing systolic murmur over the apex which was not constant. The blood pressure was: systolic, 108; diastolic, 60.

The autopsy findings were as follows: The heart weighed 395 gm. The ventricles were dilated, and both coronary arteries showed marked sclerosis and calcification. The myocardium on section showed multiple small whitish areas of fibrosis. The root of the aorta showed several yellowish calcified plaques, some of which were as much as 1 cm. in diameter.

TYPE III.—A male, aged sixty-one years, presented the following history: His past health was good. The present illness began seven years ago with a sudden attack of pain over the heart. This was attended with slight belching which brought some relief. During the past two years attacks of precordial pain had been very frequent. These usually occurred after meals or upon exertion.

The condition was more severe when he was constipated. He has never had any edema. On examination his complexion was pasty. A marked pyorrhea was present. The cardiac apex was displaced to the left; the tones were regular but distant. The lungs showed no evidence of congestion. The urine and blood were negative. Roentgen-ray examination showed the heart enlarged to the left. The patient died suddenly in an attack.

At autopsy the body was well developed and nourished. Edema and cyanosis were absent. The heart was markedly enlarged, weighing 575 gm. The valves were normal. There was a large scar on the inferior surface of the left ventricle and another on the anterior surface of the right chamber. The right coronary artery was completely obliterated in the first 2 cm. of its extent. There was also a marked narrowing of the left coronary. One of the large muscular branches, descending on the inferior surface of the left ventricle, was almost completely closed. The root of the aorta showed numerous raised yellow patches on the intima, but no calcification. *The liver was not enlarged and showed no congestion.* On microscopical examination there was extensive fibrosis in the heart. The liver was negative and the kidney showed sclerosis of a few small arterioles, which is a good evidence of hypertension.

TYPE IV.—A male, aged fifty-two years, entered the hospital with the following history. One year ago he began to suffer attacks of pain in the upper abdomen, radiating to the precordium. These often continued for as long as three hours. About six months after the onset of these symptoms he had an attack of influenza, following which his distress became more marked. He also developed shortness of breath on slight exertion and edema of the ankles. At the time of entrance to the hospital he was unable to walk 50 yards without severe distress in the upper abdomen, and marked dyspnea. On examination the patient showed all the signs of advanced cardiac failure. Cyanosis of the fingers and lips was present. There was slight edema of the chest wall and moderate edema of the extremities. The heart was enlarged, the left border extending 3 cm. outside of the nipple line. The arterial pressure was: systolic, 150; diastolic, 90. The liver was enlarged. During his stay in the hospital the patient had no attacks of pain. He died suddenly while in bed.

At autopsy the heart was definitely enlarged, weighing 550 gm. The chambers were dilated. At the apex of the left ventricle there was an area of thinning and marked connective-tissue replacement. A soft mural thrombus was attached to the endocardium covering this fibrous area. The right coronary artery showed marked calcification and narrowing. The left coronary was also severely involved and a recent thrombus was present in one of the branches. The root of the aorta presented the usual amount of senile sclerosis.

The pleural cavities showed fluid on both sides and a moderate amount was also present in the peritoneal cavity. There was a definite passive congestion of the liver and spleen.

These 4 cases illustrate the difference in the clinical picture presented. In Cases I and III the outstanding feature is the occurrence of an acute attack of pain, in one instance in the abdomen, in the other in the chest, in an individual otherwise apparently healthy. There was no congestion of the liver in either case, which further indicates that the symptoms of congestive failure which produce a restriction of activities were absent, such as effort dyspnea and edema. Cases II and IV, although attacks of pain occurred in both instances, are essentially pictures of cardiac decompensation. In Case II the heart and blood pressure are within normal limits, while in Case IV there is cardiac enlargement and the blood pressure is increased. Although coronary sclerosis is the underlying pathological change, it is apparent that each of the cases shows a somewhat different clinical picture.

Coronary Thrombosis. Of the 113 cases of coronary disease studied there was a thrombus occluding a large coronary branch in 24, or 21.2 per cent. An advanced degree of sclerosis was present in all instances. Those showing a thrombus were distributed in the four subgroups as follows:

TABLE IV.—DISTRIBUTION OF CORONARY THROMBOSIS IN FOUR SUBGROUPS.

Type.	No. of cases.
I	12
II	0
III	7
IV	5

In contrast to the uncertain and indefinite conception of the clinical manifestations of coronary sclerosis, sudden occlusion of a coronary vessel is generally regarded as possessing a definite clinical picture. Leyden[11] states that coronary occlusion is not necessarily accompanied by pain, but that dyspnea and other evidences of cardiac failure are fairly constant findings. Obrastzow and Strashesko[12] describe attacks of precordial pain associated with this condition, but point out that the principal signs are diminishing heart sounds and symptoms of heart failure. Allbutt,[2] who definitely disregards coronary sclerosis as a clinical entity, believes that coronary thrombosis has certain characteristic clinical manifestations which differ, however, from ordinary angina. The pain is often more continuous than that of ordinary angina, but the feature which he believes clearly separates coronary thrombosis from ordinary angina is the evidence of myocardial failure, such as rapid irregular pulse, weakening heart tones, dyspnea and cyanosis. Herrick,[3] in this country, has made a careful study of the sub-

ject, and divides the clinical manifestations into 4 types. His first type is characterized by sudden death. In Type II there is a sudden attack of cardiac pain, and death is deferred for several minutes to hours. In Type III the symptoms are severe and prolonged and death may not occur for days or weeks. Type IV is a hypothetical group in which the symptoms are slight attacks of pain, supposedly due to obstruction of small coronary branches. Herrick has described his third type at considerable length. The patient usually has suffered previous paroxysms of cardiac pain, but the present attack is described as the most severe and prolonged. The pain may be substernal, precordial or epigastric. Vomiting may be present. The patient is usually in collapse and the pulse rapid, small and occasionally irregular. The blood pressure is low in contrast to the usual attacks of angina. If the patient lives for a few days or weeks the signs of cardiac failure, such as dyspnea, cough and edema, follow. Twenty-three of the 24 cases of thrombosis in this series present clinical manifestations which can be grouped fairly well according to Herrick's classification and are distributed as follows: Type I, 10; Type II, 3; Type III, 10. Type IV was not taken into consideration, as all of the cases of thrombosis selected from the series were occlusions of large branches.

In the analysis of the clinical manifestations of the entire group of coronary disease, it seemed that certain of the features, described as characteristic for coronary thrombosis, occurred also in many instances where a thrombus was absent. To ascertain more definitely whether this were true, a group of 40 unselected cases of coronary sclerosis, without a thrombus, was carefully analyzed following Herrick's classification. Sudden death occurred in 20 cases corresponding to Herrick's Type I. In 13 an acute attack of pain followed shortly by death, as in Type II. In 7 instances the history was that of a prolonged attack with incomplete recovery which the patient survived for varying lengths of time, a picture which is similar to that described by Herrick as Type III. The following is an illustrative case:

The patient was a male, aged fifty-one years. His past health was good, with the exception that he had noticed some shortness of breath and slight precordial distress on exertion during the past two months. The onset of the present illness was acute, starting after his evening meal with a sharp epigastric pain and vomiting. The pain persisted through the night. On examination the following morning pain was still present; pulse was rapid, rate 130, but regular; the blood pressure was: systolic, 100; diastolic, 70. There was some tenderness over the gall bladder. The patient was seen again two days later. At this time pain was absent, but he complained of marked weakness. His heart was negative on examination except for a tachycardia. He made an attempt to be up and around, but was unable to and was forced to rest in bed. Twelve

days following the initial attack, while in bed listening to the reading of a letter, he suddenly gasped and died. The autopsy revealed the following. There was a slight edema of the ankles. The heart was normal in size, weighing 300 gm. The coronary arteries showed extensive sclerosis, being almost closed at several points, especially in the anterior descending branch of the left coronary. The right coronary was definitely involved but to a lesser degree. There was considerable fibrosis of the muscle, a portion of the anterior wall of the left ventricle being completely replaced by scar tissue. There was a marked narrowing of the vessel to this area but no thrombus. The liver weighed 1850 gm., and the centers of the lobules were prominent, indicating congestion. Interesting points in this case are the prolonged character of the pain, the incomplete recovery and the onset of signs of cardiac failure. The entire picture follows closely that which Herrick describes for Type III of coronary thrombosis. However, although an extensive sclerosis was present, there was no evidence of a thrombus. It seems justifiable to conclude from this analysis that coronary disease shows a similar clinical picture irrespective of whether a thrombus is present or not. A prolonged attack, consisting of an initial shock which the patient survives, is more frequent with a thrombus. Such a picture does occur, however, in coronary sclerosis without thrombosis. There does not seem, therefore, to be any justification for drawing any sharp distinction between these conditions. Since coronary thrombosis is constantly associated with sclerosis of the vessels, it is most reasonable to regard a thrombus not as an entity, but merely as one of the end results of coronary disease, occurring in approximately 20 per cent of the cases.

Pathological Features. Although our chief attention in this study was focused on the construction of a clinical picture, certain of the pathological findings which might have clinical significance were also noted. The data concerning the anatomical changes in the coronary arteries, the heart and the aorta were analyzed.

Coronary Arteries. The changes in the coronary arteries were of a marked degree, as this was the chief criterion for the selection of the cases. There was definite thickening of the walls with areas of marked narrowing of the lumen, and in many instances there was complete obliteration of portions of the vessels. Calcification of the walls was infrequent. Although in general, sclerosis occurred in both coronaries, there was a definite tendency for the changes to be much more extensive in the left branch. In 20 of the 113 cases, or 18 per cent, however, the degree of involvement in the right coronary was as great as that in the left, or even more marked. In the left coronary artery the branch that was most frequently and extensively involved was the anterior descending ramus, and in a number this was the only branch to show a marked sclerosis.

THROMBOSIS. A thrombus occluding one of the larger branches was present in 24 cases, or 21.2 per cent. It occurred in 22 per cent of the 45 hearts under 400 gm., and in 20.6 per cent of the 68 larger hearts. It is of interest to note that there was a marked difference in the degree of sclerosis of the coronary vessels as compared with the other arteries of the body. In many instances in which the coronary showed extensive change the other arteries, including the aorta and brain vessels, were only slightly involved. This is of some practical importance, as it indicates that one cannot judge the condition of the coronary arteries from the appearance of the vessels accessible for examination, such as the peripheral arteries or retinal vessels. In 4 cases there was a history of diabetes and a marked sclerotic change in the pancreatic artery, with degeneration of pancreatic tissue. In 2 additional cases diabetes was present, but no note was made of the condition of the pancreatic artery. Since these observations were made several clinical cases of diabetes associated with coronary disease have been seen, and it is possible that in a certain percentage a degree of pancreatic artery sclerosis sufficient to produce diabetes may occur with coronary disease.

TABLE V.—DISTRIBUTION OF HEART WEIGHT.

Heart, weight, gm.	No. of cases
200 to 299	1
300 to 399	30
400 to 499	37
500 to 599	30
600 to 699	5
700 to 799	2
800 to 899	2

MYOCARDIUM. As has already been mentioned, the heart showed some hypertrophy in a large percentage of the cases. Although there was some involvement of the right side, the preponderance of hypertrophy was in the left ventricle. In Table V the distribution of the heart weights of the entire group is given. In addition to the presence of hypertrophy, a degenerative change in the heart muscle was practically a constant finding in all of the 113 cases. This is in definite contrast to the hypertension heart without coronary sclerosis, in which such changes in the heart muscle occur only in a minimal degree. The myocardial involvement consisted chiefly of a fibrosis, which varied from a slight degree to an extensive connective tissue change. This was usually more marked in certain portions of the heart, but occasionally occurred as a diffuse fibrous infiltration. As with the coronary arteries, fibrosis was most marked in the left ventricle. The most frequent site of thinning and connective-tissue replacement was in the apex of the left ventricle. In many cases the entire thickness of portions of the ventricular wall was replaced by connective tissue. There

was no relation between the degree of fibrosis and the size of the heart. Equally extensive changes were found in hearts under 400 gm. as in those above this weight. In 16 cases, or 14.1 per cent, necrosis and softening was found in one or more areas. In 5 of these there was a rupture of the ventricular wall and in 1 a saccular dilatation in the left ventricle. The constant presence of myocardial change with coronary disease has been well shown by Clawson,[13] in a recent report. He made a careful detailed gross and microscopical study of the myocardium in 102 cases of noninfectious myocardial failure. His conclusions were that myocardial fibrosis is usually due to coronary disease and that there is a close correspondence between the location and extent of fibrosis and the distribution and degree of coronary sclerosis.

AORTA. A change of some degree was present in practically all the cases. This consisted chiefly of the presence of raised intimal patches and calcification. The involvement in the aorta, with a few exceptions however, did not seem to be any more marked than normally occurs at this age period, and could not be considered of any clinical importance. In 7 cases there was evidence of definite pathology in the aorta; 4 showed dilatation of the wall and 1 aorta had a definite thinning of the wall but no dilatation. In 2 other cases there were patches with linear depressions present, and involvement of the mouths of the coronary arteries. Lues was suspected in each of these 7 cases. Thus definite pathology occurred in the aorta in but 7 of the 113 hearts, or 6.2 per cent. This is of considerable interest in relation to Allbutt's views, for in this series the anginal type of syndrome was the outstanding clinical feature, and yet aortic pathology of any significance was present in but a small percentage. One must conclude therefore that, although lesions in the aorta may give rise to anginal symptoms, this is not the only mechanism, since coronary disease in itself is a frequent factor in the production of cardiac pain.

THE ELECTROCARDIOGRAPH. The constant finding of myocardial changes with coronary sclerosis would lead one to expect alterations in the form of the electrocardiogram. Unfortunately, there were electrocardiographical records in but 5 cases. In 4 these were definitely abnormal. In 1 the tracing was that of a bundle-branch block. In the remaining 3 there were alterations in the form of a *T* wave. This is too small a series from which to draw any conclusions. However, in a group of approximately 40 cases, which clinically would fall definitely into one or the other of the types of coronary disease discussed, electrocardiographical abnormalities occurred in about 50 per cent. This will be considered in detail in a later report.

Summary. Since there is no generally accepted conception of the clinical significance of coronary sclerosis, an attempt was made to construct a clinical picture by an analysis of a series of fatal

cases which came to necropsy. The following points are brought out by this study:

1. Coronary sclerosis is most common in males and in the age period between fifty and seventy years.

2. The outstanding clinical feature is the presence of attacks, usually of pain, less frequently of acute respiratory distress. The pain is most often in the chest, but abdominal attacks are not uncommon.

3. These attacks occur with either of the following combinations:
   (*a*) Normal sized heart, with no evidence of cardiac failure, 37.2 per cent.
   (*b*) Normal sized heart, cardiac failure present, 2.6 per cent.
   (*c*) Cardiac enlargement, congestive failure absent, 22.6 per cent.
   (*d*) Cardiac enlargement, congestive failure present, 38 per cent.

4. The clinical features of coronary thrombosis are essentially similar to those of coronary sclerosis; thrombosis, therefore, should not be considered as a clinical entity but merely as a complication of coronary sclerosis.

5. The outstanding pathological features are the following: Changes in the coronary arteries are most marked in the left branch. In addition to coronary sclerosis, thrombosis occurs in approximately one-fifth of the cases. Myocardial involvement paralleling the degree of coronary sclerosis is a constant finding. Lesions in the aorta of any significance are present in but a small percentage.

NOTE.—I am indebted to Dr. E. T. Bell, head of the Department of Pathology, for the opportunity of studying these cases.

BIBLIOGRAPHY.

1. Cited by Allbutt: Diseases of the Arteries, Macmillan & Co., 1915, **2**, 351.
2. Ibid., 1915, **2**, 353.
3. Herrick, J. R.: Clinical Features of Sudden Obstruction of the Coronary Arteries, Jour. Am. Med. Assn., 1912, **59**, 2005; 1918, **70**, 1030.
4. Romberg, E.: Krankheiten des Herzens und der Blutgefässe, Ferdinand Enke, Stuttgart, 1921, **3**, 182.
5. Hirschfelder, A. D.: Diseases of the Heart and Aorta, J. B. Lippincott Company, Philadelphia and London, 1918, p. 381.
6. Osler and McCrae: The Principles and Practice of Medicine, D. Appleton & Co., New York and London, 1922, p. 828.
7. Mackenzie, Sir James: Diseases of the Heart, Oxford Medical Publications, London, 1918, p. 313.
8. Oxford Med., 1920, **2**, 423.
9. Tice: Practice of Medicine, W. F. Prior Company, Hagerstown, Md., 1921, **6**, 253.
10. Nelson: Loose Leaf Medicine, Thos. Nelson & Son, 1920, **4**, 349.
11. Leyden, E.: Ueber die Sclerose der Koronararterien und die davon abhangigen Krankheitzustande, Ztschr. f. klin. Med., 1884, **7**, 459.
12. Obrastzow, W. P., and Strashesko, N. D.: Zur Kenntniss der Thrombose der Koronararterien des Herzens, Ztschr. f. klin. Med., 1910, **71**, 116.
13. Clawson, B. J.: The Myocardium in Non-infectious Myocardial Failure, AM. JOUR. MED. SCI., 1924, **168**, 648.

RECTAL ETHER ANALGESIA IN CHILDBIRTH.*

By James A. Harrar, M.D.,
NEW YORK, N. Y.

Lessening the suffering of the woman in childbirth by means of morphin and magnesium sulphate hypodermically, followed by colonic instillation of ether in oil, was first conceived by Dr. J. T. Gwathmey, and put in practice by him at the New York Lying-In Hospital in February, 1923. It proved to be an effective and harmless way of utilizing these familiar and inexpensive drugs, and one that could be employed by any physician without special training. With the encouragement and perseverance of Dr. A. B. Davis and the attending staff, a procedure gradually has been evolved which we are now pleased to call our standard method of obstetrical analgesia. It is this method, still unquestionably open to improvement and to be adapted somewhat to the individual needs of the patient, that I wish to present.

We have conducted the experiments with an open mind, freely criticizing among ourselves defects in technic or disadvantages that any of us could possibly note, being ready at all times to abandon it if it proved dangerous, beginning with small doses and trying various combinations until we have arrived at the routine about to be described. The procedure consists essentially in a deep intramuscular injection of one dose of morphin with magnesium sulphate in solution to prolong its action, repeating the magnesium sulphate alone, and following it in from one to two hours with a rectal instillation of ether in olive oil which is retained, employing about half the quantity of ether necessary for surgical anesthesia by rectum. The effect is a seminarcosis and amnesia, with great relief of pain, similar in appearance to the condition in "twilight sleep," and, when not used too early, without inhibiting the progress of labor, even in the perineal stage.

In the seminarcosis and amnesia produced by the use of scopolamin and narcophin, some years ago, we found we had a method that could be employed over a sufficient length of time to relieve the nervous exhaustion of labor without largely inhibiting its efficiency. The disadvantages of twilight sleep were two: A lesser disadvantage was the lack of good bearing-down pains in the perineal stage, and the increased necessity for forceps; the second disadvantage, and the greater one, was its effect upon the respiration of the child at birth. In a report published some ten years ago from the Lying-In Hospital in over 250 cases we had but 2 stillbirths, and these seemed to have sufficient obstetrical cause apart from the narcotics employed. But I think all of us now agree that

* Read before the Philadelphia County Medical Society, March 11, 1925.

with scopolamin and morphin pushed to the degree required for perfect amnesia, while we had no more stillbirths we had too many alarms, too many babies that when born gave a cough or a gasp and then lay there in an apneic state that was very disturbing. They opened their eyes, stretched their arms and legs, but did not breathe for a considerable number of minutes. These are probably the chief reasons why we have all abandoned the typical twilight sleep. However, many men throughout the country are still giving, with more or less satisfaction, a single dose of morphin and scopolamin during the first stage of labor.

With the rectal ether analgesia we do not pretend nor promise a painless labor, but great relief of suffering is experienced in a very large majority of the cases, and the patients sometimes claim marvelous results. The details of rectal analgesia are as follows:

The drugs required: 1. Magnesium sulphate with morphin. This can be procured in ampoules containing 2 cc of á 50 per cent solution of magnesium sulphate with $\frac{1}{6}$ or $\frac{1}{4}$ gr. of morphin sulphate.

2. Magnesium sulphate alone. Ampoules containing 2 cc of a 50 per cent solution are to be had.

3. The retention enema. This can readily be prepared by any druggist. It consists of:

Quinin alkaloid		gr. xx
Alcohol		♏xl
Ether		ʒiiss
Olive oil	q. s. ad	ʒiv

If the quinin alkaloid is not obtainable, the following formula may be used with equal satisfaction:

Quinin hydrobromate		gr xx
Alcohol		ʒiii
Ether		ʒiiss
Olive oil	q. s. ad	fʒiv

This, if well bottled and corked, may be kept at room temperature and is undoubtedly stable for at least a month. Should it be necessary, as it occasionally is, to repeat the instillation of the retention enema, subsequent ones should contain only 10 gr. of quinin, the other ingredients remaining the same.

4. A bottle containing 2 ounces of olive oil.

The necessary apparatus is simple. Besides a 5-cc glass hypodermic syringe with a long needle for intramuscular use, it consists of a 5-ounce funnel attached to 20 inches of rubber tubing which is in turn connected by means of a 4-inch glass connecting tip to a red rubber catheter, size 20 or 22 French. A rectal tube is too large and allows the instillation to run in too rapidly. The glass connecting tip enables the observer to note when the last of the fluid leaves the funnel.

The treatment should not be started until the woman is in active

labor. The pains should be at least at five-minute intervals and lasting at least forty seconds. The length of the contractions are best judged by placing the hand on the abdomen and timing them with the watch, as the outcry of the woman is often a poor index of the strength of the pain. Waiting for the labor to be well established thus at once eliminates cases of socalled primary inertia from treatment. In a primapara it is best to wait until the cervix is fairly well effaced and dilated to a diameter of at least two finger tips; in a multipara it can be started before this degree of cervical dilatation is reached if the pains are of the proper length and interval as described. At this time a cleansing soapsuds enema is given and this is followed with the primary deep intramuscular injection of $\frac{1}{6}$ or $\frac{1}{4}$ grain of morphin and 2 cc of 50 per cent solution of magnesium sulphate given into the gluteal region. Judgment must be used as to the soapsuds enema, as it may not be required if the customary soapsuds enema at the onset of labor has been recently given. The rectum must be both empty and quiescent to properly retain the instillation of ether in oil that is to follow the primary morphin and magnesium sulphate intramuscular injection. Experience shows $\frac{1}{4}$ gr. of morphin usually to be the proper dose, but in a small woman $\frac{1}{6}$ gr. will be sufficient. Labor should be well under way so that the morphin will not stop the uterine contractions altogether. Give the injection during an active pain when the discomfort will be least noticed. Tell the patient the object is to relieve her pain, but do not promise her a painless labor.

After this primary intramuscular injection of morphin and magnesium sulphate the patient is to be kept quiet, oiled cotton placed in the ears and the room darkened. These attentions are reminiscent of the scopolamin amnesia suggestions, but they are of undoubted value in the proper induction of any seminarcosis.

One-half hour after the primary morphin and magnesium sulphate injection we give a second intramuscular injection, consisting of 2 cc of 50 per cent solution of magnesium sulphate alone. This is given no matter whether the effect of the primary injection is sedative or not, and tends to prolong the action of the morphin.

We now come to the manner of giving and the time of the rectal instillation. It again must not be used too soon. If the effect of the morphin and magnesium sulphate is sedative withhold the instillation until the effect of the former is almost worn off. It is easier to give when the patient is still somewhat under the effect of the morphin; however, three- to five-minute intervals between uterine contractions should be present. For the beginner it is better to let the morphin and magnesium sulphate wear off entirely and to withhold the instillation until the patient is again complaining and the pains, at three- to five-minute intervals, are good and strong. If there is no relief from the morphin and magnesium

sulphate within one-half hour after the second injection, which consisted of 2 cc of 50 per cent magnesium sulphate alone, proceed with the ether instillation. The ether instillation thus rarely should be given within an hour after the first injection of morphin and magnesium sulphate. It may be from one to three hours before it is needed, depending on the patient's distress. The ideal time in a primipara is at about three finger tips' dilatation of the cervix.

It is given as follows: The contents of the bottle containing the ether mixture and the bottle containing 2 ounces of plain olive oil are warmed by letting them stand for a few minutes in warm water, first loosening or removing the corks. The patient is then placed on her left side and vaseline is liberally applied around the anus so that the ether mixture if expelled will not irritate. State to the patient just before beginning the instillation that its object is to relieve her pain and thus secure her coöperation. Tell her that during the instillation she is not to press down during pains, but to breathe deeply with her mouth open, and at all times to "draw up" with her sphincter as if she were trying to avoid expelling gas. This will tend to induce reverse peristalsis and permit the fluid to run in more readily. Pour into the funnel 1 ounce of the warm plain olive oil. Just as the oil runs out of the catheter pinch the latter near the glass connecting tip with an artery clamp. In this way all the air will be expelled from the tubing. Some of the 1 ounce of oil should still remain in the funnel. The catheter is now introduced into the rectum for about 4 inches. If the fetal head is well down in the pelvis the gloved finger must be inserted into the rectum along with the catheter to insure its passage past the head. A little of the warm ether mixture is added to the oil in the funnel, the clamp released and the contents of the funnel slowly permitted to run into the rectum. The remainder of the ether mixture is gradually added, at no time permitting the funnel to become entirely empty. Just as the last of the ether mixture is about to leave the funnel add the remaining ounce of the warm plain olive oil. Allow this to start running into the rectum and clamp the tube. It is important in order to avoid the expulsive desire that we prevent the entrance of any air bubbles into the rectum. Now make pressure on the anus with a towel during two or three contractions, leaving the pinched catheter in place meanwhile, then gently withdraw the catheter. Should a uterine contraction intervene during the instillation simply make pressure against the anus with a folded towel and let the funnel act as the escape reservoir. Continue to make pressure over the anus during three or four contractions after the catheter is out. All these details are important and the successful retention of the instillation largely depends on the meticulous care with which it is given.

A third intramuscular injection of 2 cc. of 50 per cent solution

magnesium sulphate alone is then given immediately to prolong the action of the ether. The patient may now turn upon her back or assume whatever position is most agreeable to her. The same quiet is maintained as before. Do not make a vaginal or rectal examination too soon after the instillation or the instillation will be expelled. Do not be misled by the quiet behavior of the patient into thinking she is having very slight contractions or none at all. Within fifteen or twenty minutes you can smell ether on her breath, she becomes flushed and occasionally has a little of the excitability of the first stage of ether anesthesia, but never to the extent of requiring restraint.

The patient is drowsy and sleeps lightly between the pains, but consciousness is not entirely lost. She responds somewhat tardily to questions and usually obeys commands as to change in posture. When a uterine contraction occurs she manifests her suffering to a greater or less degree and again dozes. Occasionally the casual observer would have the impression that there was very little amelioration of the pain, the patient complaining and restless during the contractions, and yet afterward we find the amnesia secured to have been as definite as that after scopolamin. Frequently the patient confesses of her own volition that she remembered very little after the rectal instillation was given.

The obstetrical side of the case and the progress of labor must be closely watched, for the presenting part frequently is bulging the perineum without any apparent increase in effort on the part of the patient. Functional abnormalities must be discovered and corrected as they arise, and the mechanism of labor followed and managed as thoroughly as though no analgesia were being employed.

When the effect of the first ether instillation has worn off, that is, when the patient again complains of pain, which is usually in from two to three hours, a second, or even a third, rectal instillation may be given at intervals of three hours or more. The first instillation is given containing 20 gr. of quinin alkaloid; in subsequent instillations only 10 gr. Each subsequent instillation is accompanied with one intramuscular injection of 2 cc of 50 per cent magnesium sulphate. Contrary to some authorities we are convinced that the quinin is absorbed by the rectum, as evidenced by the occasional complaint of buzzing and ringing in the ears or slight deafness after the labor. We tried 30 cases, omitting the quinin entirely, and found the omission of the quinin caused definite second stage and perineal delay. Dr. Losee, of the hospital laboratory, has now definitely proved the rectal absorption of quinin by its qualitative recovery from the urine in 45 out of 50 parturients.

A minimum of inhalation ether is needed for the delivery, and the anesthetist must be cautioned about this. Frequently no additional anesthesia is needed even for a perineorrhaphy. Chloroform should never be used with the ether rectal instillation. Gas, if

desired, is safe and very satisfactory as an adjuvant anesthetic for the delivery.

Relief of pain in labor is always open to two serious objections: the prolonging of the labor and the endangering of the safety of the mother or her baby. We believe this method, of all procedures we have so far studied, to be the least likely to prolong the labor if not used too early, and in over 2000 trials in the past two years to have been without danger to either mother or child. It can be used both in normal labors and in cases of dystocia, in labors induced with bags, in toxemias, in cardiacs and in women in labor with acute pulmonary conditions to whom inhalation anesthesia might be disastrous.

We find that it is applicable in hospital practice in 70 per cent of all labors. This is twice the applicability of scopolamin amnesia in our hospital experience ten years ago. Those not getting the rectal analgesia are largely on account of inexpedience, such as brief labors, admission with the head on the perineum or on account of some administrative interruption in the service. In other words, there is no obstetrical contraindication to the treatment after active labor is initiated. It can be used in the home with equal facility and with equally good results, and does not require the services of a trained anesthetist, especially taking the place of gas anesthesia in the last three hours of labor. The out-patient staff at the hospital are using it with good effect in the tenement confinements. It perhaps does not carry the patient along as thoroughly or as continuously as morphin-scopolamin amnesia, but it gives more relief than any form of inhalation analgesia with which I have had experience. It is not dangerous to the baby, though if pushed to the degree of complete anesthesia, which is not the desired object of the treatment, the baby may be born rather deeply anesthetized. We find no increase in operative deliveries; in fact in some comparative series it seemed proved that the use of forceps was decreased. There has been no increase of postpartum hemorrhage and no increase in the stillbirth rate.

There are certain occasional annoyances—I cannot call them disadvantages—of the method to which I must refer. Most of them are due to faulty technic. The most evident of these is occasional expulsion of the rectal instillation. Close attention to all the details of giving the retention enema will obviate its loss in bulk. The frequent extrusion of small quantities of light-yellow, sour-smelling liquid fecal matter, making it more difficult to keep the field clean in the perineal stage will not occur if the cleansing soapsuds enema is completely expelled before giving the rectal instillation. In some cases nausea is present, but not as commonly as after inhalation etherization. Patients at times will complain of a slight burning sensation in the anal region immediately after the rectal instillation. The liberal use of vaseline will prevent this,

though it sometimes may be due to an unrecognized fissure. Now and then there is some distention of the colon with gas but not to any serious degree. Rarely the patient has a diarrhea during the first twenty-four hours postpartum. I have already alluded to the occasional first stage of ether excitement but I have never seen it to the extent of requiring restraint.

There is never any tender induration after the magnesium sulphate injections such as we see after mercurial injections. To date there have been 5 abscesses. Two of them occurred when we were using 6 cc in bulk of the magnesium sulphate solution at one time, and 2 occurred after giving the injection in the thigh over the fascia lata, a location especially susceptible to abscess after any hypodermic. Considering the thousands of injections we have given, we are satisfied that, given intramuscularly with aseptic technic, the magnesium sulphate solution will rarely cause any abscess or necrosis *per se*.

If the primary injection of the morphin and magnesium sulphate is given too early it may temporarily stop the labor, but we have all seen morphin alone do the same thing when we have given it to ease the parturient's suffering while the cervix dilated. If this does occur, when the labor starts again the whole cycle of analgesia is started again, waiting until the pains recur at at least five-minute intervals and lasting over forty seconds, and the cervix is at least two finger tips' dilated before beginning again with the morphin and magnesium sulphate injection. Remember also to be very light with the inhalation ether at the perineal stage, as the patient goes under readily with a minimum amount and the baby may be born deeply anesthetized if much inhalation ether is given the analgesized mother.

Variations in the scheme will occur to men who use the rectal analgesia as their experience with it widens. With very large women, or when the ether instillations has no effect or even excites the patient and the birth is anticipated within two hours, a second instillation of one-half the original amount may be given at once. At times in nervous primiparæ, or where for some reason we would like to start the analgesia before the pains and the cervical dilatation had attained the desired stage, $\frac{1}{8}$ gr. of morphin can be given with the first 2 cc of magnesium sulphate solution, and in one-half hour a second $\frac{1}{8}$ gr. of morphin with the second 2 cc of magnesium sulphate, then waiting for the strong pains and three finger tips' dilatation of the cervix before giving the ether instillation by rectum.

Summary. We are convinced that this is the safest and most effective method for the relief of the pains of childbirth over a period of hours that has so far been devised. Its applicability is much greater than that of scopolamin amnesia. It can be used safely and effectively by the physician in home confinements, and does not require the services of a trained anesthetist. The drugs

required, morphin, magnesium sulphate, ether and quinin, are easily obtained and well known in their action. The quinin is found to be an essential ingredient in the rectal instillation formula. The only contraindication to the procedure is uterine inertia, and the only restriction is not to start too soon. The woman must be in active labor, that is, pains every five minutes, lasting forty seconds by the watch, and in a primipara preferably the cervix should have attained a dilatation of two or more finger tips. The mechanism of labor must be as closely followed by the obstetrician as if no analgesia were being employed.

This method of analgesia and amnesia does not carry the parturient woman entirely over the valley of her suffering on any soft couch of unconsciousness, and it would be a great mistake to believe it did or to promise her that it would. But we do feel assured that we have here a method of real value that will abolish the most dreadful part of the ordeal of labor in almost all cases, that it is without danger to either the mother or her baby, and that in painstaking hands by strictly adhering to the described technic, even its occasional annoyances may be avoided.

REPORT OF AN INTERESTING TYPE OF DIAPHRAGMATIC HERNIA OF THE CARDIA OF THE STOMACH THROUGH THE ESOPHAGEAL ORIFICE.*

By Julius Friedenwald, M.D.,

and

Maurice Feldman, M.D.,

Baltimore.

(From the Gastro-enterological Clinic of the Department of Medicine, University of Maryland.)

Hernia through the diaphragm is a deformity which has always attracted much interest. Ambroise Paré[1] was the first, in 1610, to describe 2 cases due to trauma; following this publication Fabricus Hildamus[2] reported another instance in 1646. The first congenital case noted in literature was observed by Riverius,[3] in 1698, and Kirschbaum[4] described this condition exhaustively in 1755, reporting 17 cases. Later (1769) Morgagni[5] published a monograph on diaphragmatic hernia and Sir Astley Cooper[6] presented an interesting account of this affection in 1824. More recently Bowditch[7] (1853) contributed a valuable monograph on this subject, collecting 88 cases from the literature.

* Read by title at the Meeting of the Association of American Physicians held in Washington, May 7, 1925.

The most satisfactory classification of diaphragmatic hernia, as described by Richards,[8] is as follows:

I. True hernias (those with hernial sac).
   1. Congenital.
   2. Acquired.
      (*a*) Through the natural openings (esophageal).
      (*b*) Elsewhere (traumatic or nontraumatic).

II. False hernias (those without hernial sac).
   1. Congenital.
   2. Acquired (all traumatic).

III. Eventration of diaphragm.

The various locations for diaphragmatic hernia may be divided, according to Richards, into anterior, central, posterior, esophageal and others.

1. ANTERIOR. These forms of hernia, also known as parasternal hernias, are located on either side of the attachments of the diaphragm to the sternum and are produced through Larry's space, or the foramen of Morgagni.

2. COSTAL. This form of hernia may or may not present a sac and appears at areas not related to the fusion lines of those parts combining to form the diaphragm.

3. POSTERIOR. These are largely due to an absence in the closing of the pleuroperitoneal canals, and originate in the lumbar region at or near the foramen of Bochdalecki.

4. ESOPHAGEAL. This is a very frequent site for diaphragmatic hernia. It is due to the failure of the muscle surrounding the diaphragm to closely encircle the esophagus. These hernias are frequently the true forms, the sac being formed of part of the diaphragm attached to the esophagus.

5. OTHER SITUATIONS. Of less frequent occurrence are those forms that have their exit by way of entrance of the sympathetic nerves in the crura of the diaphragm.

It is neither our object in this communication to discuss the various forms of diaphragmatic hernias, nor indeed those occurring through the esophageal hiatus in which a large part or the whole of the stomach is found in the thoracic cavity, but to limit our attention to that type in which the cardia of the stomach in part or in whole has herniated through the esophageal opening. Hernia through the esophageal hiatus is not uncommon, and occurs more frequently than any other form. In most instances the stomach enters the left chest or posterior mediastinum covered by a hernial sac. In the vast majority of cases reported the whole or a large part of the stomach, and even the other abdominal viscera may be included. Abbott[9] has recently called attention to the true but small hernias of the diaphragm, especially of the periesophageal type, which may be detected in the early stages, and in which the cardia is alone involved, and Morrison[10] has pointed out the method

of diagnosis by means of roentgenology. Many of these hernias are acquired and are produced by unusual strain or coughing. They are frequently only detected by means of fluoroscopy.

Of interest in regard to this special type of hernia is the following observation of Andrew[11] made in 1903 on a case discovered in the dissecting room of Aberdeen University, which represents the first case published of diaphragmatic hernia of the cardia, through the esophageal opening.

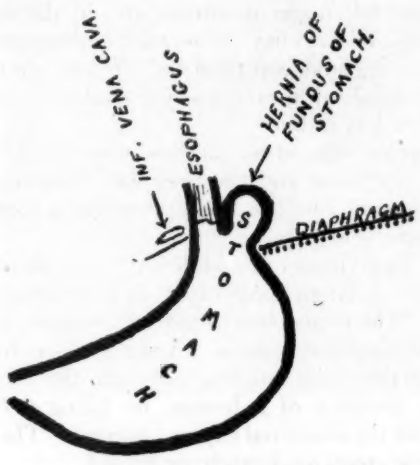

FIG. 1.—Diagrammatic drawing showing herniated fundus of stomach through the esophageal opening.

The patient was a female in whom the stomach presented a hernia at the cardiac orifice. Immediately to the left of the esophageal opening there was a dome-shaped pouch of the diaphragm into which a finger could easily be passed, and drawn up into this was part of the cardiac end of the stomach measuring vertically about an inch. The herniated cardia could easily be pulled down from this pocket, when it was noticed that the part of the stomach wall which lay against the neck of the pouch was thickened. The peritoneum was reflected from the diaphragm to the stomach at the top of the pouch.

There were 6 cases of diaphragmatic hernia of the cardia of the stomach through the esophageal orifice in our series. These were all observed in females, the ages ranging between forty-one and sixty-two years. The symptoms noted were quite similar to those which will be referred to later, and the diagnosis was definitely established by means of the roentgen-ray which revealed the typical picture of this anomaly.

The following notes briefly describe the salient features of our cases:

Case Reports. CASE I.—July 18, 1924: M. M., a female, aged sixty-two years, was referred to us by Dr. I. Pels. She was affected with an extensive lupus erythematosus for the past ten or eleven years. There was present, in addition, marked indigestion. Eight years ago the patient had been subjected to severe attacks of abdominal colic occurring in the upper right quadrant of the abdomen, for which hypodermatic injections of morphin became necessary for relief. She now complains of abdominal pain, noted especially in the left upper quadrant and in the epigastrium, loss of appetite, nausea, acidity, eructations, regurgitation of food, occasional vomiting and constipation. These symptoms are more prominent following full meals, and occur more frequently at night after the patient has retired.

On examination the chest organs were found normal. The abdomen was distended and the liver was somewhat enlarged and tender on pressure. The test meal presented a total acidity of 33; free hydrochloric acid, 22.

The roentgen-ray report is as follows: The heart and lungs are negative. The esophagus presents a slight retardation of the meal at the cardia. The stomach is in normal position, and held slightly to the right; peristalsis is normal. A shadow is noted at the cardia, extending into the chest, passing through the esophageal orifice, indicating the presence of a hernia; no filling defect is revealed. The pylorus and the duodenal cap are normal. The liver is slightly enlarged and the colon moderately prolapsed.

CASE II.—October 17, 1924: M. S., a female, aged fifty-three years, had been the subject of nervous and hysterical attacks for a long time. During the past year there has been marked indigestion in the form of pain in the epigastrium and immediately above the ensiform cartilage, with a burning sensation in the stomach occurring about an hour following meals. There were present acid eructations, loss of appetite, regurgitation of food and constipation. The symptoms were aggravated in the recumbent position, especially following large meals. Occasionally dysphagia was noted, and a sensation of a lump moving up an down during deglutition was experienced. This patient has lost 35 pounds in weight.

On examination the chest organs are found normal. The abdomen is relaxed and soft, and no masses or tender areas are noted. The gastric secretion presents a total acidity of 34; free hydrochloric acid, 20.

The roentgen-ray examination reveals the heart and lungs to be negative. The stomach is in normal position and peristalsis is normal; no filling defects are noted. In the recumbent position a small pouch of the cardia of the stomach is observed above the diaphragm, passing through the esophageal orifice. The lower end of the esophagus is observed behind and to the right of the herniated

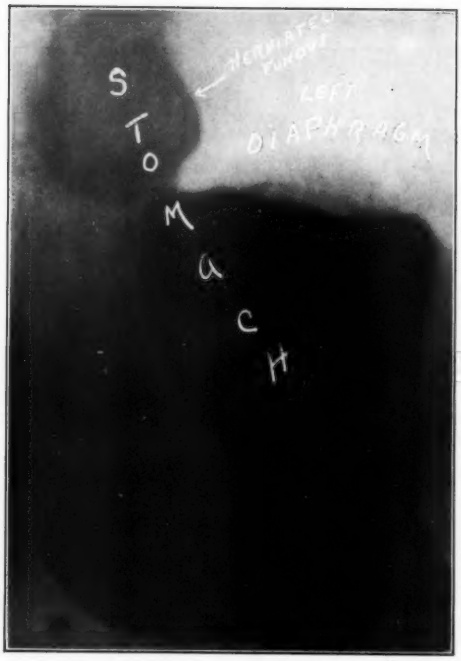

FIG. 2.—Case No. V. Showing hernia of the stomach, esophagus to right of stomach.

FIG. 3.—Case No. II. Hernia of the stomach, esophagus to right of hernia.

FIG. 4.—Case No. IV. Showing herniated stomach above diaphragm, esophagus behind hernia.

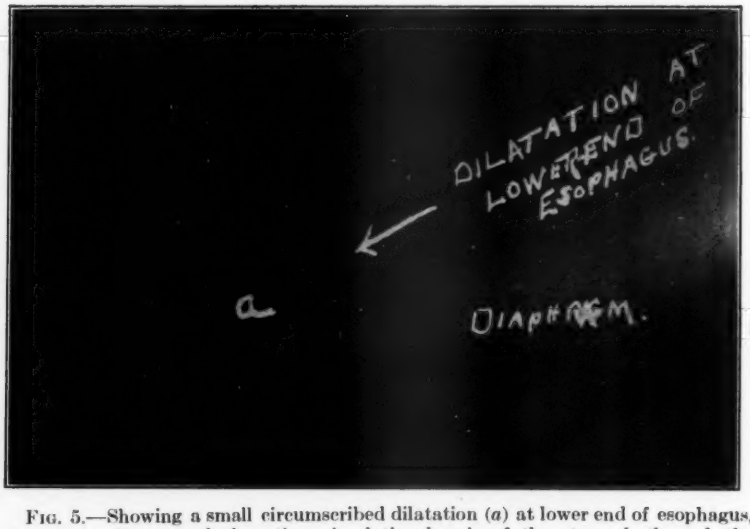

FIG. 5.—Showing a small circumscribed dilatation (*a*) at lower end of esophagus, due to a stricture and ulceration, simulating hernia of the stomach through the esophageal opening.

cardia. The pylorus and duodenal cap are normal. The liver extends to the costal margin. The colon is moderately prolapsed.

CASE III.—November 5, 1924: N. C., a female, aged forty-two years, had been affected for a number of months with discomfort in the epigastrium just below and above the ensiform cartilage. At times actual pain is experienced, especially following a heavy meal, and during the night the discomfort is often sufficiently severe to awaken the patient. She is also affected with acidity of the stomach; regurgitation of food and occasionally vomiting, dizziness and constipation. Dysphagia has frequently occurred, especially in the early morning and following food.

On examination the thoracic organs are found to be normal. The abdomen is relaxed, the edge of the liver being just palpable; no tenderness is noted anywhere except slightly in the upper left quadrant. The gastric secretion presented an achylia; total acidity, 33; free hydrochloric acid, 0.

The roentgen-ray examination is as follows: The esophagus presents a slight retardation of the barium meal at the cardiac orifice. The stomach is in normal position; the pylorus and duodenum are normal. In the recumbent posture the cardia of the stomach is observed to pass up through the esophageal orifice on deep inspiration, which disappears when the patient is in the upright position.

CASE IV.—December 12, 1924: C. S., a female, aged fifty-six years, has complained for the past year of pain in the epigastrium and of indigestion occurring about an hour following meals. There is marked acidity and regurgitation, and the symptoms frequently become aggravated at night during the sleeping hours. Difficulty and pain in deglutition are occasionally noted. On account of these symptoms, together with a painful epigastric area, a diagnosis of ulcer was made; however, no improvement followed the institution of an ulcer treatment.

On examination the chest organs are found to be normal. The abdomen is soft; the edge of the liver is palpable, and there is an exquisitely tender area in the epigastrium just below the ensiform cartilage and a slight tenderness is also noted under the right costal arch. The gastric secretion shows a total acidity of 55; free hydrochloric acid, 36.

The roentgen-ray examination reveals a slight retardation of the barium meal at the cardia; no irregularity of the lumen of the esophagus is noted. In the recumbent position the cardia of the stomach is observed passing up through the esophageal opening only, however, in deep inspiration, or on straining, the meal passing behind the shadow. The hernia is absent in the upright posture.

CASE V.—January 5, 1925: J. I. G., a female, aged forty-one years, for some months following an indiscretion in diet, has complained of discomfort in the lower left chest and epigastrium, occurring especially one-half to one hour following meals. In addition, dysphagia, nausea, acid eructations, flatulency and constipation have occurred at times.

On physical examination the thoracic organs are found to be normal. The abdomen is distended; there are no enlargements. There is a slight tenderness noted on pressure above the ensiform cartilage, extending into the epigastrium.

The gastric secretion reveals a total acidity of 40; free hydrochloric acid, 25.

The roentgen-ray presents a slight retardation of the barium meal at the cardia. The stomach shows normal peristalsis, and the pylorus and duodenal cap are normal. In the recumbent posture the cardia of the stomach is observed as a hernia through the esophageal hiatus about the size of a silver dollar. It becomes more marked on deep inspiration and disappears in the upright position. The meal can be detected passing around the herniated shadow.

CASE VI.—April 2, 1925: N. C., a female, aged fifty-three years, had a cholecystostomy performed six years ago, and a cholecystectomy four years. She has since been affected with eructations of gas, pyrosis, distention in the upper abdomen appearing especially about two hours following meals. Attacks of pain occur most severely at 11 P.M. and 2 A.M. The symptoms become markedly aggravated by a heavy diet, especially when the latter consists of meat. The patient is extremely neurotic.

On physical examination the thoracic organs are found negative. The abdomen is markedly distended and very pendulous. There is a slight epigastric pulsation, with tenderness over the entire abdomen, but especially noted in the left upper quadrant.

The roentgen-ray report is as follows: The heart and lungs are negative; the esophagus is normal, with the exception of the presence of a patent cardioesophageal opening. In the recumbent posture the opaque meal passes quickly down through the esophagus. On deep inspiration, a small knuckle of the cardia is also noted passing through the esophageal hiatus under similar conditions. The hernia disappears in the erect posture.

These small hernias give rise to a train of symptoms suggesting this anomaly with signs somewhat pointing to gastric ulcer or cholelithiasis. These consist of epigastric pain or pain immediately above the ensiform cartilage associated with acid eructations, regurgitation and vomiting. The symptoms are more frequent following the ingestion of large meals and occur more often when the patient assumes the recumbent posture after eating. The discom-

fort may be especially severe at night, causing the patient to be suddenly awakened from sound sleep. Dysphagia is not infrequent, especially early in the morning, and there is often a sensation as if food were passing part way up the esophagus and then to return again. The pain appears usually an hour or two following meals, especially on reclining, and is relieved temporarily by means of alkalies. It often radiates to the back between the shoulder blades. The disappearance of symptoms for variable periods may erroneously point to ulcer, while the acute pain radiating to the back may suggest cholelithiasis.

The diagnosis may be definitely established by means of the roentgen-ray examination which presents a very characteristic picture. However, in the routine examination of the gastrointestinal tract this type of hernia may be entirely overlooked unless a special technic be instituted. The patient is at first fluoroscoped in the upright posture. The opaque meal is carefully observed as it descends through the esophagus. A slight retardation of the meal may be noted at the cardia in some instances. The lumen of the esophagus, however, appears quite normal. In this condition the stomach is situated largely to the left and usually high under the left side of the diaphragm, and is of the cow-horn or modified cow-horn type. In the upright position no abnormality is noted, and no clue as to the actual condition is obtained. In the examination the patient is placed in the recumbent posture in various positions in order to obtain the clearest view of the cardio-esophageal opening. Even under those conditions, however, the hernia through the esophageal opening may not become visualized until rapid and deep breathing has been practised. Under certain conditions it may also be advisable to have the patient strain. By means of this method, due to the more constant filling of the fundus the herniated area becomes more easily visualized.

On expiration the opaque meal may be noted passing back into the stomach below the diaphragm. In our cases a portion of the fundus of the stomach was observed passing up through the esophageal opening through the diaphragm on deep inspiration, and then only when the patient maintained the recumbent posture. The size of the hernia varied in our cases from that of a chestnut to a small orange. A fluid level or a bubble was frequently present, but was ordinarily noted in most instances after the diagnosis of hernia had been established. The contour of the herniated fundus is usually smooth and regular in appearance. This form of hernia occurs to the left of the esophagus and may not be visualized in every examination. The constancy depends largely upon several factors: (1) Upon the size of the esophageal orifice; (2) upon the muscular contraction around the esophageal opening; (3) upon the position of the patient; (4) upon deep inspiratory movements; (5) upon the special roentgen-ray technic described above. According

to Morrison,[10] the cardioesophageal opening is usually patent in this condition, though this only occurred but once in our series. Neither stasis in nor strangulation of the herniated sac was noted in any of our cases.

In the diagnosis of diaphragmatic hernia of this type other affections simulating this condition must be ruled out. On this account the patient is given another opaque meal through a straw while in the recumbent posture, and the esophagus is examined under the fluoroscope while swallowing the barium mixture. By means of this method it is a simple matter to ascertain the relation of the herniated fundus to the esophagus. The esophagus is observed on either side or posterior to the hernia. In establishing the diagnosis this procedure is of great importance.

At times a small circumscribed dilatation at the cardiac orifice of the esophagus will simulate this condition. However, under the fluoroscope the dilatation is observed within the esophagus and above the diaphragm while the patient remains in the recumbent posture. Obstruction may be present, though this condition was not observed in a case presenting a small dilatation in our clinic in which the shadow was situated directly above the diaphragm, resembling a hernia in many respects.

Again, when patency of the cardioesophageal opening occurs, which is also best noted in the recumbent posture, the opaque meal will be observed passing up the esophagus on deep inspiration, the stomach appearing below the diaphragm.

A diverticulum at the lower end of the esophagus also may be confused with this form of hernia. The pouch may be observed budding off from the esophageal wall and the filling takes place directly from the esophagus. A gastric diverticulum as a pouch protruding from the wall of the stomach when occurring directly below the diaphragm also may resemble this condition.

The form of thoracic stomach as described by LeWald[12] must not be confused with diaphragmatic hernia of this type. In this condition the esophagus is shortened and never passes through the esophageal opening while the stomach remains constantly in the thoracic cavity.

Conclusions. 1. There exists a form of hernia of the cardia of the stomach, through the esophageal opening, in which this area is alone involved, producing a rather characteristic picture which may even be demonstrated in its early stages.

2. These hernias often give rise to a train of symptoms suggesting atypical forms of ulcer or cholelithiasis.

3. The diagnosis may be definitely established by means of the roentgen-ray, which presents characteristic signs only; however, when the patient is examined in the recumbent posture in deep inspiration or on straining.

4. In all cases presenting atypical signs of ulcer or cholelithiasis a thorough investigation should be instituted in order to determine the possibility of the presence of this condition.

REFERENCES.

1. Ambroise Paré: Opera Chirurgica ab Ambrose Pareo, Frankfort 1610; ch. **30**, p. 230.
2. Fabricus Hildamus: Opera Gulielmi Hildami, Frankfort 1646; cen 2; obs. **33**, p. 108.
3. Riverius Lazari, Rivieri: Opera Medica Universa, London, 1698; Obscent quart ob. 67.
4. Kirschbaum: Dissertation Chirurgie Lusanne, 1755, **3**, 217.
5. Morgagni: Seats and Causes of Diseases, Letter, 1769, 54.
6. Astley Cooper: Treatise on Hernia, London, 1824.
7. Bowditch, H. I.: Treatise on Diaphragmatic Hernia, Jewett Thomas & Co., Buffalo, 1853.
8. Richards: Ann. Otology, Rhinology and Laryngology, 1923, **32**, 1145.
9. Abbott: Jour. Am. Med. Assn., 1924, **83**, 1898.
10. Morrison: Jour. Am. Med. Assn., 1925, **84**, 161.
11. Andrew: The Lancet, 1903, i, 792.
12. LeWald: Radiology, 1924, **3**, 91.

IODIN HYPERTHYROIDISM.

Conclusions Based on a Study of 38 Cases.

By Arnold S. Jackson, M.D.,
Section in Surgery, Jackson Clinic,
Madison, Wis.

The popular enthusiasm which has supported the prophylactic treatment of simple colloid goiter, together with the discovery of the efficacy of iodin in the treatment of exophthalmic goiter, has greatly increased the number of cases of iodin hyperthyroidism in this country within the past two years. Between January, 1923, and January, 1925, 38 cases of iodin hyperthyroidism have been observed in our Clinic. Of this number 20 have been observed during the last six months. In view of the apparently rapidly increasing number of patients observed with this condition, attention should be directed to the danger in the use of iodin, as well as to its beneficial effects in the treatment of goiter. I have felt this more keenly than ever since my recent observation of 2 patients, whose death was directly due to the ingestion of iodin. Moreover, many of these patients have been brought through their serious conditions with the greatest difficulty.

Etiology of Iodin Hyperthyroidism. Although the beneficial effects of iodin in the treatment of goiter have long been realized, it remained for Kocher to call attention to the possible dangers in this form of therapy. Röser, Prévost, Lebert and others believed

that hyperthyroidism was caused by the softening of the goiterous tissue and not by iodin intoxication; but this view was not accepted at once. Rilliet described a syndrome which he termed *constitutional iodism* and considered due to certain goiterous subjects receiving iodin. Because in many ways this condition resembles exophthalmic goiter, or Basedow's disease, Breuer called it "iodin-Basedow," and it has since generally been termed by that name. From time to time mention has been made in the literature of the danger of using iodin promiscuously in the treatment of goiter, and occasional reports of isolated cases appeared. Recently I made a preliminary report of 18 such cases studied over a brief period of time.[4] The rapidly increasing number of these patients at present justifies a more careful study and a detailed report.

In considering the question of etiology, it has been noted that many kinds and preparations of iodin have been responsible for the development of iodin hyperthyroidism. The various liquid forms of the syrup or tincture, preparations containing ferrous iodid, or the tablet form have all been used. There have been interesting observations regarding the dosage. Apparently some persons have a relative immunity to iodin hyperthyroidism, since iodin administered in moderate or even large doses for weeks or months causes no toxic symptoms. Others develop toxic symptoms very rapidly after the ingestion of small doses or after only a few weeks' administration. I have been surprised in many of my cases at the small amount of iodin necessary to initiate toxic symptoms.

The Pro and Con of General Distribution of Iodin. The variable quantity of iodin necessary to produce toxic symptoms in persons with adenomatous goiters brings up the question of the advisability of the wholesale distribution of iodin by way of drinking water or table salt. The Michigan State Board of Health, after a very careful analysis of the problem has given every school child this year iodized salt.

Certain cities, for example, Rochester, New York, Minneapolis and Chicago, have considered putting iodin in the city drinking water. As a means of preventing the further development of goiter, and as a method of combating the colloid goiter now in existence, these methods are certainly a step in the right direction. One question, however, naturally arises: What effect will this wholesale use of iodin have on the hundreds of thousands of persons with adenomatous goiter now living in the goiter areas. It is contended by some that the amount of iodin these persons would receive would be too infinitesimal to produce any harmful effect. Others go so far as to say that the great good that would result would outweigh any harm that might be done. It is also contended that since goiter does not occur in the south where iodin is prevalent in the water, an effort should be made to rectify the conditions in the goiter areas and change the iodin content of the water at once.

The objection to the distribution of iodin in the form of salt is that the dosage is very inaccurate. Some children use a great amount of this commodity, while others use but little. A child may take a great deal of salt one day and then go several days without any. If salt is employed in the cooking, as is advocated by some, any or all members of the family will receive iodin in various amounts.

De Quervain believes that the general prophylaxis by means of cooking salt, so as not to be harmful to adults with goiter, should be restricted to a minimum dose, even though it be insufficient for an infant already affected. He is opposed to the free distribution of iodin, as there is great risk of "Graves' disease."

With regard to supplying iodin through the drinking water, O. P. Kimball writes: "Following the publication by McClendon last spring of his findings regarding the deficiency of iodin in the water, the Department of Health of Rochester, N. Y., attempted to iodize the city water supply by the addition of such an amount of sodium iodid as would make each 5 gallons of water contain 1 mg. of sodium iodid. This method had often been discussed, but it had never been considered practicable because of the great waste. For instance, only approximately one-fourth of 1 per cent of the city's water supply, not more than 4 ounces, is actually imbibed, and not more than 15 per cent of this 4 ounces is really needed. That means that the city is paying $450.00 for a needed 5 gm. of sodium iodid."

Whether or not such small doses of iodin are sufficient to initiate symptoms of hyperthyroidism in cases of nontoxic adenoma is a debatable problem. Careful study and detailed reports on all such cases as may be observed will solve this question.

Effect of Iodin in Various Types of Goiter. We know from the experience of Marine and Kimball, as well as that of others, that iodin administered to children under twenty years of age for the prevention or treatment of colloid goiter is practically harmless when given in small doses. During the past three years I have had over 300 cases of colloid goiter in children under observation, and there has been no instance of the development of toxic symptoms.[5] When iodin is administered in the presence of an adenoma in children I believe great care must be exercised. I frequently give iodin in such cases with no hope of eradicating the adenoma but merely with the idea of retarding its growth by putting the gland at rest until the patient has reached the age of twenty-one years. Although I never give these patients more than 10 mg. of iodin a week, I have had 2 cases of beginning hyperthyroidism which were aborted by discontinuing the iodin at once and placing the patient at rest. I have observed several other patients treated elsewhere with much larger doses of iodin. One of these was a girl, aged fifteen years, who lost 30 pounds in two months and had a metabolic

rate of +45 per cent. I performed a thyroidectomy after medical measures had failed, and she made an excellent recovery.

On the whole, iodin hyperthyroidism is rarely observed in persons under thirty years of age. I believe that iodin is of no avail in treating goiter, except the exophthalmic type, after the age of twenty-one years, and that with increasing age it is employed with added risk.

Iodin is certainly very definitely contraindicated after the age of twenty-one years, in the presence of an adenomatous goiter. Yet, there are now thousands of persons with this form of goiter who are taking iodin either by means of some patent medicine, or, alas, under a physician's directions. The newspapers and magazines are so full of articles on iodin and goiter that the laity has come to consider one a cure for the other. Every patient who has a goiter comes to the physician with hopes of a cure by iodin. In many cases the physician fails to distinguish between a colloid and an adenomatous goiter, or even between an adenomatous and an exophthalmic goiter. If a slight reduction in the size of the neck through the effect of iodin on the colloid occurs, there is such gratification that the symptoms of developing hyperthyroidism are overlooked.

Differential Diagnosis of Adenomatous and Exophthalmic Goiter. The term iodin-Basedow, as applied to the peculiar syndrome developing from the injudicious use of iodin in the treatment of goiter, is not a correct one in the light of our present knowledge of the subject. At the time when Breuer described this condition, no attempt had been made to distinguish between the form of hyperthyroidism occurring in exophthalmic goiter, or Basedow's disease, and the hyperthyroidism of toxic adenoma. It was not until 1913 that Plummer pointed out the chief differences between the two conditions.

Whereas, exophthalmic goiter is a disease of rapid onset, averaging nine months' duration and occurring most frequently in young persons, toxic adenoma is a chronic condition averaging four years in onset and occurring as a rule in persons more than forty years of age. In exophthalmic goiter the symptoms of hyperthyroidism progress by series of waves at the crests of which all the symptoms are exaggerated and a crisis occurs. In toxic adenoma the hyperthyroidism progresses insidiously and slowly, causing a permanent damage to the heart, kidneys and other organs. There is a rapid loss of weight and strength, accompanied by a variable appetite which, in exophthalmic goiter, at times is ravenous. Likewise, examination reveals exophthalmos in fully 50 per cent of the cases within three months of onset. The gland is symmetrically enlarged and thrills and bruits may be detected in 80 per cent of cases. Exophthalmos does not occur in adenomatous goiters; the gland is asymmetrically enlarged; thrills and bruits are seldom noted.

Hypertension occurs in this type of goiter with a proportionately high diastolic pressure, in contrast to a slightly elevated systolic and a low diastolic pressure in exophthalmic goiter. In adenomatous goiter, not only is there slow development of the toxic symptoms, but there is usually a history of goiter of sixteen years' duration or more. The metabolic rate is considerably lower, seldom rising above + 60 per cent, while in exophthalmic goiter we not infrequently see rates above + 100 per cent.

Syndrome of Iodin Hyperthyroidism. The syndrome of iodin hyperthyroidism is not typical of either adenomatous or exophthalmic goiter, and yet presents many symptoms common to both. It may develop in children as young as ten years or in elderly persons who have adenomatous goiter. It is uncommon before the age of thirty years, the average age of the patients in this series being thirty-five years. The same tremor, loss of weight and strength, tachycardia, restlessness and insomnia occur, as in the two types just described. The onset of symptoms and the loss of weight are more rapid and severe than in toxic adenoma, and thus iodin hyperthyroidism rather closely resembles exophthalmic goiter. The peculiar type of nervousness, at times approaching delirium, is also like that of exophthalmic goiter. The average duration of symptoms in this series was about three months.

Two patients in this series lost more than 50 pounds in two months. The ravenous appetite characteristic of exophthalmic goiter does not occur. Tachycardia is severe and persistent, and there is little or no response to digitalis. Apparently the iodin exerts a toxic, antagonistic effect on the myocardium that renders it immune to the action of this drug. The pulse often rises above 150 after thyroidectomy and is the source of much concern. Thrills, bruits and exophthalmos do not occur in these cases. The pulse pressure is elevated, but the blood-pressure findings closely resemble those in toxic adenoma. The same is true of the basal metabolic rate, the average in this group being + 31 per cent as compared with + 29 per cent in a group of cases of toxic adenoma and + 54 per cent in a series of cases of exophthalmic goiter.

Treatment of Iodin Hyperthyroidism. If iodin hyperthyroidism is diagnosed early in its course, it is possible to abort the toxic symptoms. Three of the patients here reported were cured by medical measures, while the rest were relieved only by thyroidectomy. If the symptoms are not becoming progressively worse every effort should be made to improve the patient's condition first by medical means.

Operation in cases of iodin hyperthyroidism is frequently performed with considerable risk. One patient (No. 42044) was delirious for a week following operation. Another (No. 42282) gave a history of having been given iodin for four months by a physician. During the two months preceding and following child-

birth she lost 55 pounds. She was admitted in a state of delirium, running a temperature of 102° C. and a pulse rate of 140. After two

FIG. 1.—Case No. 42044. Gross specimen, showing areas of colloid with multiple degenerating adenomas of the thyroid. The absence of the typical, beefy appearance of a hyperplastic gland is evident.

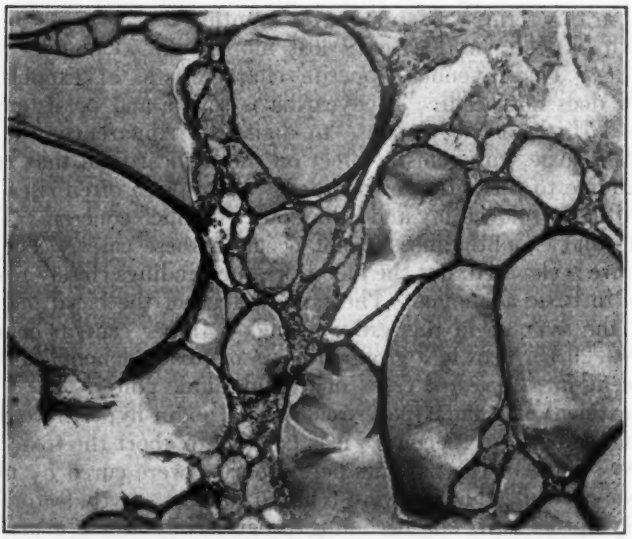

FIG. 2.—Case No. 42282. Large areas of colloid in an adenomatous thyroid. The apparently benign appearance is in no way indicative of the severe clinical picture of hyperthyroidism induced by iodin with fatal termination.

weeks' treatment there was marked improvement, only to be followed by a more critical course. Thyroidectomy was attempted as a last resort, but a fatal termination followed three days later.

FIG. 3.—Case No. 42282. Degenerating, fibrous, hyalin adenoma with areas of colloid. The clinical picture was one of extreme hyperthyroidism, with delirium, marked tachycardia and emaciation accompanied by gastrointestinal crises. The basal metabolic rate of + 54 did not indicate the severity of the disease.

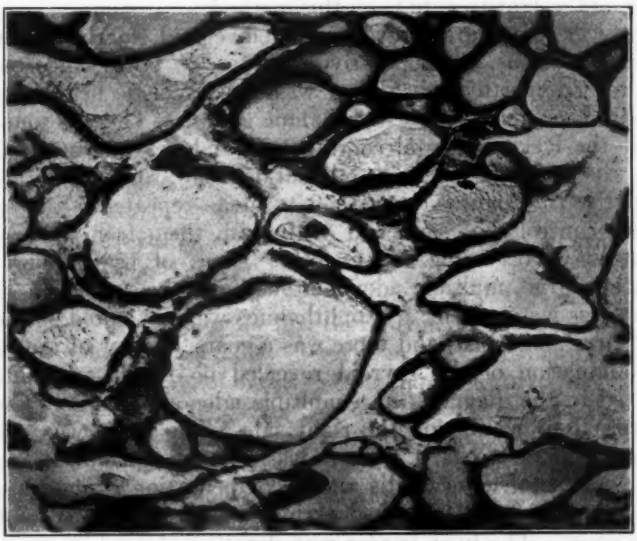

FIG. 4.—Case No. 30262. Apparently large areas of colloid in an adenomatous goiter. Close inspection reveals a small amount of hypertrophy, but the typical columnar cells of exophthalmic goiter are absent. The clinical findings in this patient were somewhat suggestive of the latter condition, but the history of the ingestion of iodin under a druggist's prescription for several months confirmed the diagnosis of iodin hyperthyroidism.

This patient remained in delirium; the pulse continued irregular and never fell below 150.

A careful pathological study as usual in these cases failed to reveal any of the typical findings of exophthalmic goiter. There were no areas of hyperplasia and only the typical appearance of an adenomatous goiter with areas of colloid was observed.

The prognosis in iodin hyperthyroidism following thyroidectomy is excellent in the early cases, inasmuch as little permanent damage has been done to the heart and other vital organs.

Typical Case of Iodin Hyperthyroidism. CASE 42044.—A man, aged sixty-four years, came to our clinic complaining of stomach trouble. The symptoms were of three months' duration, and dated from an accident in which he had been run over by a side delivery rake and painfully bruised. Since then he had had frequent spells of vomiting during or immediately after eating. Sweet foods had caused the most trouble. The vomiting had been increasing in severity and frequency. No hematemesis or melena had been noted and he had had no pain. He had lost between 40 and 50 pounds in two months, and had become too weak to walk. Increasing nervousness had been noticed, with palpitation of the heart, especially on lying down. After some hesitation the patient admitted having taken ten bottles of Allen's Goiter Cure during the past three months.* The patient had noticed a goiter for three years and sought to cure it by this method.

Physical examination revealed an emaciated elderly man whose restless, nervous, uncoöperative manner at once suggested the picture of hyperthyroidism, but was characteristic neither of that of toxic adenoma nor of exophthalmic goiter. (There is something about the lack of mental coördination and nervous instability in these cases verging on or into actual delirium, together with a sort of apathy that causes the patient to moan repeatedly and lose all mental control that serves to distinguish them from the nervous disturbances occurring in the other types of hyperthyroidism.) A rather large, multiple adenomatous goiter was visible. Edema of the legs was evident. Exophthalmos was not noted. The skin was warm and moist, and there was a coarse tremor of the fingers.

Examination of the thyroid revealed no thrills or bruits and resulted in the diagnosis of a multiple adenomatous goiter with a substernal projection on the right side. The heart was enlarged 2, on a scale of 1, 2, 3, 4. There was a hemic murmur at the apex and evidence of myocarditis and decompensation. The pulse was 130, and there was a marked arrhythmia, as frequently noted in these cases. The liver border was slightly enlarged; there were a

* The writer sent a bottle of this remedy to the Propaganda Department of the American Medical Association in 1923. Investigation in the Association's chemical laboratory revealed that the nostrum consists essentially of ferrous iodid and hydriodic acid in syrup.

few moist rales at both bases of the lungs posteriorly; the abdomen was negative on palpation. With the exception of infected teeth, the physical examination was otherwise negative. The blood pressure was 160 systolic and 66 diastolic; a high pulse pressure with the systolic normal and the diastolic decreased.

A tentative diagnosis was made of iodin hyperthyroidism in an adenomatous goiter.

Roentgen-ray examination of the stomach was negative. The urine was normal, save for hyalin casts, 1. Examination of the blood was negative. The basal metabolic rate was + 67.

In the hospital proctoclysis was employed and subcutaneous injections of saline were administered in an effort to dilute the toxins and to combat the dehydration. Digitalis was prescribed. Although it has been repeatedly noted that digitalis has little effect on the pulse rate, it may strengthen the cardiac muscle. Luminal and chloral were used to combat the nervousness. Little or no improvement was noticed at the end of ten days, except that the vomiting was controlled; there was no dehydration; the mental attitude was better. Nothing was to be gained by delaying operation further.

Thyroidectomy was performed under the usual morphin-scopolamin-novocain method of anesthesia. The patient, however, was not as quiet and coöperative as patients with other types of hyperthyroidism. As usual, following operation in these cases the pulse became extremely rapid, remaining as high or higher than 150 for four days. Arrhythmia persisted for two weeks. For a week the patient was delirious much of the time. The temperature, however, differed from that customarily observed in cases of postoperative hyperthyroidism in exophthalmic goiter, and did not rise above 102° C.

Two months later the patient had regained 20 pounds; his strength had returned; the pulse rate was 80; the nervousness had disappeared. Save for slight edema of the ankles, he was apparently well.

Pathology. Medical literature contains little that is enlightening concerning the pathology of the thyroid gland in cases of hyperthyroidism induced by iodin. Crotti makes the following statement with which I cannot agree. "We know that in iodin-Basedow the histological changes are the same as the ones seen in any other form of toxic or bacterial thyroiditis. Hyperemia of the gland takes place; cellular hypertrophy and hyperplasia occur; the thick colloid, rich in iodin, undergoes liquefaction and is quickly absorbed and thrown into the circulation under the form of an iodized albuminoid substance, mostly thyroxin."

A careful pathological study of my cases failed to reveal the occurrence of cellular hypertrophy and hyperplasia. Instead of the colloid being absorbed, it is evident from the microphotographs,

as well as the gross specimens, that unusually large areas of colloid are present in the thyroid. The typical multiple adenomatous goiter was found, with degenerating and degenerated cystic, fibrous, hyalin and calcareous adenomas. In three of the sections minute areas of hyperplasia containing cells of the columnar type, such as may be seen in cases of toxic adenoma of the thyroid, were present.

MEDICAL AND SURGICAL RESULTS IN TREATMENT OF IODIN HYPERTHYROIDISM.

Case No.	Sex.	Age.	Iodin, months.	Prescribed by.	Basal metabolic rate.	Loss in weight in pounds.	Treatment.	Basal metabolic rate on discharge.	Gain in weight.
32444	F.	65	3	Fam. phys.	+29	10	Thyroidectomy	+5	40
32860	F.	28	5	Fam. phys.	+17	12	Thyroidectomy	+1	24
31732	F.	30	2	Fam. phys.	+20	25	Thyroidectomy	+4	8
29894	F.	36	3	Fam. phys.	+44	29	Thyroidectomy	+10	25
30160	F.	34	2	Fam. phys.	+13	16	Thyroidectomy	+4	28
33276	F.	27	3	Surgeon	+22	15	Medical	+4	5
33663	F.	53	2	Fam. phys.	+29	30	Thyroidectomy	+0	50
33275	F.	23	2	Internist	+16	8	Thyroidectomy	+4	14
34808	F.	35	2½	Quack remedy	+31	13	Thyroidectomy	+8	22
29598	F.	50	3½	Specialist	+46	15	Thyroidectomy	+4	18
34592	F.	32	4	Quack remedy	+24	10	Medical	+8	12
35087	F.	40	3	Fam. phys.	+18	30	Thyroidectomy	+4	16
35365	F.	52	4	Fam. phys.	+51	50	Thyroidectomy	+5	51
35280	F.	52	3	Fam. phys.	+30	25	Thyroidectomy	+6	24
35351	F.	35	2	Quack remedy	+26	14	Thyroidectomy	+3	20
35267	F.	37	3	Internist	+40	23	Thyroidectomy	+6	22
36687	F.	38	4	Fam. phys.	+28	8	Thyroidectomy	+5	20
36589	F.	28	3	Fam. phys.	+28	10	Thyroidectomy	+5	13
38914	F.	22	3	Fam. phys.	+30	10	Thyroidectomy	+6	10
40173	F.	47	2½	Fam. phys.	+52	13	Thyroidectomy	+10	25
39915	F.	45	3	Fam. phys.	+55	13	Thyroidectomy	+0	10
42044	M.	64	3	Quack remedy	+67	51	Thyroidectomy	+8	42
42282	F.	38	4	Fam. Phys.	Too sick	53	Thyroidectomy	Died	
42959	F.	49	4½	Fam. phys.	+62	35	Medical	Died	
31596	F.	18	2	Fam. phys.	+22	10	Thyroidectomy	+10	8
39042	F.	27	8	Quack remedy	+47	13	Thyroidectomy	+2	13
35280	F.	52	3	Physician	+30	25	Thyroidectomy	...	27
39419	F.	30	2	Druggist	None	5	Medical		
39882	F.	30	12	Physician	+40	0	Thyroidectomy	0	15
41177	F.	41	1	Physician	+20	10	Thyroidectomy	+3	10
41288	F.	39	2	Physician	+25	0	Thyroidectomy	−3	5
40064	F.	49	1	Physician	+18	18	Thyroidectomy	−8	30
30262	F.	27	2	Relative	+57	16	Thyroidectomy		
41412	F.	14	3	Physician	+24	10	Thyroidectomy	0	16
27035	F.	36	3	Physician	+24	6	Thyroidectomy	+7	5
41278	F.	25	4	Physician	+28	8	Thyroidectomy	+4	6
40586	F.	14	3	Quack remedy	+46	20	Thyroidectomy	+11	25
31596	F.	16	8	My own	+21	6	Medical	+5	6

The significance of these hyperplastic areas in only three of the specimens examined is not sufficient to warrant considering them pathognomonic of iodin hyperthyroidism. Their importance in toxic adenomas has not yet been explained.

If there is any change in the histological structure of the thyroid gland in cases of iodin hyperthyroidism, it is not evident from a study of these cases. There was nothing to distinguish the gross or microscopical appearance of the gland from either a toxic or a nontoxic adenomatous goiter.

The adenomas are enveloped in a thick capsule of fibrous connective tissue. Microscopically, these nodules are seen to be made up of irregular alveoli of various sizes, lined with flat cuboid epithelium. Some of the alveoli are filled with colloid. The alveoli may be closely packed together, presenting a picture of pressure atrophy, or separated by considerable stroma.

While the pathological picture of iodin hyperthyroidism in no way differs from that of the nontoxic or toxic adenomatous type of goiter, it is of course markedly different from either the purely colloid and exophthalmic forms. The typical, beefy, meaty appearance of the latter type, with its alveoli composed of epithelial hyperplasia without colloid, is in marked contrast to the soft translucent appearance of colloid goiter, whose acini are distended with colloid.

Probably this type of hyperthyroidism can best be accounted for on a physiological basis. Since it has apparently been impossible to explain on a pathological basis, it may be concluded that there is a disturbance in the iodin metabolism. Crotti asserts that the gland in these cases contains a lesser amount of iodin than the normal thyroid or any other form of goiter. This much we know, that iodin hyperthyroidism is concerned only with the adenomatous type of goiter, and does not occur in the purely colloid type.

I believe that adenomas develop in a colloid goiter as a form of compensatory hypertrophy. When the thyroid gland becomes overworked and can no longer supply the body cells with the thyroxin they demand it deposits an incomplete product in the form of colloid, which gives rise to socalled adolescent goiter. In a further effort to supply the demands of the body the thyroid gland is stimulated to form new cells which give rise to adenomatous tissue. Consequently, when iodin is administered in small amounts to children whose thyroids contain small adenomas and a large amount of normal tissue the embarrassment of the gland may be relieved, and thus the tendency of the gland to multiply and form new adenomatous tissue may for a time be checked. When iodin is given in too large amounts to children, or when it is prescribed for adults in whom the amount of normal thyroid is decreased through the degenerative action of the adenomatous tissue, the iodin metabolism of the gland is disorganized. Instead of taking up iodin and

converting it into thyroxin to supply the demands of the body cells, the thyroid is apparently unable properly to metabolize the iodin which is in circulation either in excessive amounts or as an incomplete toxic product.

That there are numerous other views that might serve to explain this phenomenon is evident. Until the pathologists are able to explain to us the various pictures seen in simple adenomas, toxic and exophthalmic goiter, as well as in iodin hyperthyroidism, the true explanation of these conditions will be obscure. Even the etiology of the adenomatous type of goiter is a matter of conjecture. Crile and others maintain that the adenoma does not arise as a form of compensatory hypertrophy in a neglected colloid goiter, but, rather, from a fetal rest. Probably studies in physiological chemistry, such as Kendall's brilliant work, will bring us close to the real solution of these problems.

Conclusions. The number of cases of iodin hyperthyroidism has greatly increased, due to the popular demand for iodin in the treatment of goiter.

In the series of 38 cases reported in this article 20 were observed within the past six months. Two cases terminated fatally.

This condition had generally been termed *iodin-Basedow* in the literature, and consequently has been confused with exophthalmic goiter.

Iodin should not be distributed promiscuously either in water or salt, but should be administered in exact amounts and under a physician's order.

Even minute amounts of iodin are sufficient to initiate symptoms of hyperthyroidism in certain persons with adenomatous goiters.

Iodin should be administered with particular care to children with adenomatous goiters; it should never be given to adults with this condition.

Every child in the goiter belt between the ages of ten and twenty years should receive small weekly doses of iodin for the prevention or treatment of colloid goiter.

Iodin hyperthyroidism is rare in persons under thirty years of age. It develops only in the presence of an adenomatous goiter. The clinical syndrome may be clearly distinguished from that seen in toxic adenoma or exophthalmic goiter. Thrills, bruits and exophthalmos do not occur.

If an early diagnosis is made medical treatment may abort the toxic symptoms. Thyroidectomy is indicated when the condition does not yield to medical measures.

The pathological picture is not characteristic. Grossly, the gland has the typical appearance of an adenomatous goiter containing degenerated, cystic, fibrous and calcareous encapsulated nodules. Colloid may be seen in large amounts. The microscopical picture shows acini of variable size, lined with flat, cuboid cells, and filled

with colloid. Fetal acini and occasional small areas of hypertrophic cells are found.

REFERENCES.

1. Breuer, A.: Beitrag zur aetiologie der Basedow'schen Krankheit und des Thyreoidismus, Wien. klin. Wchnschr., 1900, **13**, 641.
2. Crile, G. W.: Personal communication, November 23, 1924.
3. Crotti, A.: Thyroid and Thymus, Philadelphia, Lea & Febiger, 1922.
4. Jackson, A. S.: Iodin as a Cause of Hyperthyroidism, with a Report of 18 Cases, Journal-Lancet, 1924, **44**, 324.
5. Jackson, A. S.: Observations Based on 300 Cases of Colloid Goiter, Wisconsin Med. Jour., 1924, **23**, 149.
6. Kimball, O. P.: Michigan Public Health, February, 1924.
7. Kocher, T.: Ueber Jodbasedow, Arch. f. klin. Chir., 1910, **92**, 1166; Verhandl. a. d. Gesellschaft f. Chir., 1910, **39**, 82.
8. Lebert, H.: Die Krankheiten der Schilddrüse und ihre Behandlung, Breslau 1862, p. 220.
9. Marine, D., and Kimball, O. P.: Prevention of Simple Goiter in Man, fourth paper, Arch. Int. Med., 1921, **23**, 661.
10. McClendon, J. F., and Hathaway, J. C.: Inverse Relation Between Iodin in Food and Drink and Goiter, Simple and Exophthalmic, Jour. Am. Med. Assn., 1924, **82**, 1668.
11. Plummer, H. S.: The Clinical and Pathological Relationship of Simple and Exophthalmic Goiter, Am. Jour. Med. Sci., 1913, **146**, 790.
12. Prévost: Kyst suppuré du corps thyroïde, Bull. Soc. de méd. prat. de Paris, 1881, p. **118**.
13. De Quérvain, F.: Goiter: A Contribution to the Study of the Pathology and Treatment of the Diseases of the Thyroid Gland, New York, Wm. Wood & Co., 1924.
14. Rilliet, F.: Exposition et réfutation de la théorie du docteur Rœser sur la cachexie goîtreuse; nouvelle confirmation de la réalité de l'iodisme constitutionnel, mémoire posthume, Gaz. hebd. de méd., 1861, **8**, 621.
15. Rösser: Ein Beitrag zur Kropf-cachexie, bisher fälschlich Jodkrankheit genannt, Med. Cor.-Bl. d. Wurttemb. ärztl. Ver., 1860, **30**, 257.

REVIEWS.

A PRACTICE OF GYNECOLOGY. By HENRY JELLETT, M.D., F.R.C.P.I., Consulting Obstetrician to the Department of Health of New Zealand; Consulting Gynecologist, Rotunda Hospital, Dublin; Ex-Master, Rotunda Hospital. Fifth edition. Pp. 726; 417 illustrations (many in color) and 15 colored plates. Philadelphia: Lea & Febiger, 1925. Price, $8.50.

ALWAYS an excellent text for student and practitioner, clear and concise in its diction, well illustrated and reflecting strongly the sound surgical principles and technical ingenuity of the author, this edition maintains its previous standing as one of the best single-volume treatises on gynecology.

The revision includes ample discussion of the work of Sampson on implantation adenomata; of Rubin's gas inflation of the Fallopian tubes; Novak's writings on menstruation; ovarian transplantation; the newer ideas regarding sterility; roentgenotherapy and vaccine treatment have been rewritten. The chapters on surgical principles and technic are up to date, with excellent correlation of the illustrations. P. W.

LABORATORY DIAGNOSTIC METHODS. A Manual for Physicians, Medical Students, and Laboratory Technicians; by JOHN A. KOLMER, Professor of Pathology and Bacteriology in the Graduate School of Medicine of the University of Pennsylvania and Pathologist to the Medico-Chirurgical and Polyclinic Hospitals, and FRED. BOERNER, Associate in Bacteriology in the Graduate School of Medicine of the University of Pennsylvania. Pp. 338; no illustrations. New York: D. Appleton & Co., 1925.

THIS manual presents in an outline form brief directions in the technic of the various laboratory tests. It includes sections on Clinical Pathology, Bacteriology, Serology, and Blood Chemistry. The first section represents a revision of the Manual on Clinical Pathology by Pepper and Kolmer issued twelve years ago. This is the most helpful section since the methods lend themselves

best to the style of presentation used. The methods described are essentially those employed in clinical pathology, bacteriology, and serology in the Department of Pathology and Bacteriology of the Graduate School of Medicine in the University of Pennsylvania and its Medico-Chirurgical and Polyclinic Hospitals. The book unfortunately contains some typographical errors, which unless recognized by the experienced, would tend to impair the results of such tests as the macroscopic agglutination of antigens of B. typhosus, and the complement-fixation test in tuberculosis. J. S.

MANSON'S TROPICAL DISEASES. Edited by PHILIP H. MANSON-BAHR, D.S.O., M.A., M.D., D.T.M. and H. (CANTAB.), F.R.C.P. (LOND.), Physician to the Hospital for Tropical Diseases, London, and the Albert Dock Hospital; Lecturer at the London School of Hygiene and Tropical Medicine. Eighth edition. Pp. 895; 453 illustrations. New York: William Wood & Co., 1925. Price, $11.00.

SINCE the publication of the seventh edition of this work tropical medicine has had to deplore the death of one of its foremost pioneers, Sir Patrick Manson, the original author of this textbook. It needs no introduction to the profession, since it has been for a generation the *vade-mecum* of practitioners in the tropics. Under the capable guidance of Dr. Philip H. Manson-Bahr, the book has been thoroughly revised and brought abreast of the latest developments in this field. The subject matter is clearly yet concisely stated, keeping in mind the original plan of the volume that it be adequate in information yet of a handy size to meet the exigencies of travel and of tropical life. The book is well and profusely illustrated. May its career in the future be as illustrious as it has been in the past. R. K.

DISEASES AND DEFORMITIES OF THE FOOT. By JOHN JOSEPH NUTT, B.L., M.D., F.A.C.S., Professor of Orthopedic Surgery, Polyclinic Medical School and Hospital; Surgeon-in-Chief, New York State Orthopedic Hospital for Children; Orthopedic Surgeon, Willard Parker Hospital, Nyack Hospital and Rockland County Hospital; Member of the American Orthopedic Association. Second edition. Pp. 309; 105 illustrations. New York: E. B. Treat & Co., 1925.

THIS book is not intended as a textbook, but for practical advice to the general practitioner for information concerning the care of the diseases and deformities of the foot. The author gives splen-

did description of the more common conditions and acceptable forms of modern treatment. The opening chapters present excellent study of the anatomy and physiology followed by the method of examination. Such subjects as Schaffer's foot, weak foot, flat foot, club foot, Pott's paraplegia, cerebral paralysis and infantile paralysis are interestingly described with the various forms of treatment and a brief description of the operations for the deformities following these conditions. The text is excellently illustrated.

D. W.

THE EFFECTS OF IONS IN COLLOIDAL SYSTEMS. By DR. LEONOR MICHAELIS, University of Berlin, at present Professor of Biochemistry at the Aichi Medical University in Nagoya, Japan. Pp. 108. Baltimore: Williams & Wilkins Co., 1925.

THIS monograph is a compilation of the material presented by the author in his lectures in this country last year. The origin and behavior of electrical fields surrounding colloidal particles are treated from a theoretical standpoint, emphasis being laid upon the effect of dissolved salts in the liquid phase. These studies are a closer approach to a true knowledge of such phenomena as agglutination, adsorption at cell surfaces and many others, and therefore exert a strong influence on modern biologic research. B. O.

PHYSICAL DIAGNOSIS OF DISEASES OF THE CHEST. By JOSEPH H. PRATT, A.M., M.D., and GEORGE E. BUSHNELL, PH.D., M.D. Pp. 522; 166 illustrations. Philadelphia: W. B. Saunders Company, 1925.

THAT the authors have made a praiseworthy attempt to produce a book on physical diagnosis of diseases of the chest based on physical laws and pathology is easily recognized in this book; but their effort has only been partially successful. There are two parts to the book, one on the lungs, the other on the heart, and to be fair the reviewer should deal with each separately. The former is far less satisfactory than the latter. There is no subject which requires more careful and lucid writing than the description of physical signs and the details of physical diagnosis. In this respect Part I of the book is much at fault. Furthermore, in a scientific work such statements as the following are, to say the least, dangerous and misleading: One page 159, in a discussion of asthma, "Because the patients of the second class do not respond to cutaneous sensitization tests it does not necessarily follow that the condition of their lungs is not in some measure due to or aggravated by the

elimination, by way of the respiratory passages, of food poisons which gouty or arthritic subjects are not able to dispose of otherwise." Or on page 224, "All old persons likewise become more or less tuberculous, or more accurately, the universal tuberculization manifests itself more distinctly in the old than in younger persons." Nor would one expect such a complete acceptance of "arthritism" as the cause of pulmonary hemorrhage, "if the hemorrhage was due to arthritism the bronchi will soon be found to be absolutely dry." For the medical student the statement that if the supraclavicular gland or glands be found enlarged the presumption is that the enlargement is due to tuberculosis also seems of very doubtful value.

Part II of the book is excellently written and not open to the criticisms which apply to Part I. If bound separately it would be a very valuable book for practitioner or student, but it suffers from being mated with Part I and the book as a whole cannot be recommended for any purpose.

Nor do the publishers escape all criticism. Misprints on pages 12 and 19 and a frequent failure of type alignment deserve mention. Illustrations are numerous, but the vast majority of them are not original and almost a half are taken from German sources, some with the old-fashioned Latin markings, others with German abbreviations. One might at least hope by this time we would be spared an illustration of the old Riva-Rocci sphygmomanometer. The book's heart is good but its lungs are sadly deficient and its prognosis must therefore be very serious.

PROCEEDINGS OF THE INTERNATIONAL CONFERENCE ON HEALTH PROBLEMS IN TROPICAL AMERICA. Held at Kingston, Jamaica, B. W. I., July 22 to August 1, 1924, by invitation of the Medical Department, United Fruit Company. Pp. 1010; 61 illustrations. Boston: United Fruit Company, 1924.

To any one interested in tropical medicine this volume will be of the greatest interest. The seventy papers which it includes touch practically every phase of tropical medicine, and represent the thought of acknowledged leaders in this field. R. K.

MODERN SURGERY. By JOHN CHALMERS DA COSTA, M.D., LL.D., F.A.C.S. Pp. 1483; 1200 illustrations. Philadelphia: W. B. Saunders Company, 1925.

THIS is the ninth edition of this work and a perusal of the publisher's page shows revisions and reprints too numerous to mention.

The above sentence is the best recommendation with regard to the value of this most excellent surgery. Anyone at all familiar with surgery anywhere in the world recognizes the value of any work produced by the author.

The book is up to the minute as regards surgical matters, written in a pleasing style, concise, to the point and good for reference for surgeons, practitioners and students.

I can heartily recommend it as being an extremely good one-volume surgery. E. E.

LUMBAR PUNCTURE. By MARTIN PAPPENHEIM, M.D., Professor at the University of Vienna; Medical Superintendent of the Neurological Department, Municipal Infirmary, Vienna. Translated by GEORGE CAFFREY. Pp. 248; 9 illustrations. New York: William Wood & Co., 1925. Price, $5.00.

THIS book offers an exhaustive presentation of lumbar puncture, beginning with its history and including its technic, diagnostic value and therapeutic applications. The various methods of investigation applied to the cerebrospinal fluid are described in detail. There is a short appendix on encephalography and puncture of the cisterna. The book is well written and the translation is in the main well done. The technic of cisterna puncture, however, might have been more clearly described, perhaps with the aid of an illustration. R. K.

RECOVERY RECORD (FOR USE IN TUBERCULOSIS). By GERALD B. WEBB, M.D., Consulting Physician, Cragmor, Glockner and Sunnyrest Sanatoria; President, Colorado School of Tuberculosis; and CHARLES T. RYDER, M.D., Cragmor and Glockner Sanatoria; Colorado School of Tuberculosis. Second edition. Pp. 81; 106 temperature charts. New York City: Paul B. Hoeber, Inc., 1925.

To daily temperature blanks is prefixed an excellent outline of the essentials of treatment and the hazards and hopes of the "cure." Many and apt quotations incite to a widening knowledge of the limitations tuberculosis imposes, and to a philosophy which will make the handicap tolerable. Mental rest is properly emphasized. The tone is hopeful. The high mortality is, we think, best driven home by personal talks, adapted to the individual, but always unequivocal. F. McP.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE.

ROGER S. MORRIS, M.D.,

TAYLOR PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI.

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

The Relation of Infection to Diabetic Coma.—In this report by GEORGE GRAHAM (*Quart. Jour. Med.*, 1925, **18**, 294) nothing new is brought out in reference to the etiology of diabetic coma, but there is stressed a point which is frequently overlooked in the management of patients suffering from diabetes who go into coma without any apparent cause. The factor that is responsible for the development of the acidosis, leading to coma in patients who have been satisfactorily progressing under insulin therapy, is in the great majority of cases some infection. This infection at times is perfectly obvious but in a certain number of cases it is only found with difficulty. To illustrate his thesis Graham mentions 9 patients with coma. In 2 of the patients no infection could be found; in 2 the infection was plain; in 2 of the patients there was no obvious infection on admission but in whom a definite lesion would have been found at an autopsy if the patient had died in coma; and in 3 there was no sign of any other infection and who "would probably have shown no lesions of other disease at an autopsy if the patient had died in coma, unless the examination had been very complete." Under this last caption is included a case of infection of the antrum of Highmore, a case of mild influenza and one of otitis media. In diabetics with a general or local infection, insulin is much less effective in lowering the blood sugar than when the individual is infection-free and is much more likely to go into coma. The hypothesis that seems most satisfactory to the author to explain this phenomenon is that during infection there is an increased demand for insulin because of the increase in the metabolism.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL AND NORTHEASTERN HOSPITALS.

Symptoms Observed in Nontraumatic Diaphragmatic Hernia.—HEALY (*Am. Jour. Roentgenol*, 1925, **13**, 266) noted that the most constant symptom was substernal pain with regurgitation when in the supine position. The next in order is the vague gastric distress, sometimes with tenderness referable to the right upper quadrant and not in the epigastric region, accompanied at times by pain radiating to the back similar to a gall stone attack. Then came vomiting in the morning with hyperacidity. Dyspnea, with palpitation of the heart, was not so common. Only in a very few cases did the author note difficulty in swallowing. Nontraumatic diaphragmatic hernia of the fundus of the stomach is much more common than formerly thought. It is extremely important to make early diagnosis, especially of the smaller type of diaphragmatic hernia, on account of the misleading symptoms which might be the cause of needless operations, also the danger of incarceration with its high mortality. The roentgenologist can help determine the type of treatment by observing the size of the hernia, the symptoms when the hernial sac is filled and the amount of dilatation of the esophagus. He can also suggest the site of operation whether above or below the diaphragm, by determining the position of the diaphragm, the width of the angle at the ensiform and the extent of ossification seen in the costochondral cartilage.

Cancer Infection.—OCHSNER (*Surg., Gynec. and Obst.*, 1925, **40**, 335) states that cancer in the beginning always appears as a circumscribed growth. While in this stage it positively can be cured permanently if a sufficient amount of the surrounding tissue is taken out, to insure the total removal of cancer. At first cancer increases by invading the surrounding tissues. Later metastases are formed by the transportation of infected cells from the original growth to distant parts of the body, through the lymph channels of the blood. For a time these infected cells may be interrupted in their journey by intervening lymph nodes. The removal of the original growth, together with all of the infected lymph nodes may still result in a permanent cure. This can be accomplished with greater certainty if the removal is carried out with cautery. The incidence of cancer is greatest in persons above middle age. It is practically confined to persons living in civilized communities. Domestic animals living in civilized communities also become infected with cancer. Wild animals are free from it. Cancer rarely occurs in skin covered by clothing. Filth

applied either externally or internally influences the occurrence. Clean skins are rarely the seat of cancer, as shown in the case of Japanese who take daily hot baths. Persons eating vegetables grown in soil fertilized with human excrement suffer largely from cancer of stomach and colon. The natives of the tropics and the arctic regions are equally free from cancer. These two classes live on food not contaminated with manure or human excrement. The actual cause of cancer has not been established to the satisfaction of all who are entitled to an opinion. Heredity seems to have a definite relation to the development of cancer in that it at least provides a predisposition or lack of immunity. Cancer in plants has been proved to be due to the Bacillus tumefaciens, by Erwin F. Smith, of the United States Laboratory of Plant Pathology. John Nuzum has isolated a filterable micrococcus from many cancers in man and in animals. The same micrococcus has been isolated from cancer produced artificially.

The Early Diagnosis of Cancer of the Large Bowel.—HOMANS (*Boston Med. and Surg. Jour.*, 1925, **192**, 695) declares that nothing could well be more harmful to progress in the treatment of cancer than the belief that strictly internal cancers can seldom, if ever, be identified early enough in their course to be cured by surgery. Constipation, associated with well established colic and distention, is a late symptom of cancer and patients who have reached this stage would be rarely cured, if it were not for the well known tendency of adenocarcinoma of the colon to metastasize late. It is a moderate or intermittent constipation, associated perhaps with indigestion and discomfort, which is under particular consideration in this condition. In the right side of the colon, symptoms suggestive of subacute appendicitis, tending to appear in attacks in which the constitutional and local signs are less marked than the patient's sensations suggest. There is possibly local soreness or distention of the bowel and quite probably since tumors in this region are often cellular and bleed easily, a noticeable degree of anemia. In the transverse colon there are attacks of low abdominal cramps or colic, sometimes associated with vomiting and in a majority of instances some degree of constipation. Not infrequently there is freedom from constipation and discomfort between attacks. In the descending colon and sigmoid flexure, there are either of two types of symptoms—a type marked by mild attacks of gaseous discomfort and low abdominal cramps, sometimes but not necessarily associated with a moderate degree of constipation and another type marked by steadily increasing constipation ending in obstruction. In the rectosigmoid there are symptoms similar to those due to obstruction in the sigmoid proper, but tending evermore to constipation and to the presence of blood upon the stools.

A General Survey of Radiotherapy in Malignant Disease.—SCOTT (*Brit. Med. Jour.* 1925, **1**, 596) says that the primary growth is but an indication that the patient has malignant disease and does not by any means give a correct idea of its extent. To insure the plan of attack being developed on sound lines, it must be based on the assumption that malignant disease is a generalized disease and not a local lesion. The author maintains that if primary growth can be destroyed by radiation,

metastases will be equally susceptible, possibly to a much smaller dose for they are usually less bulky. Some radiologists advocate the high, others the low voltage technic. A better distinction would be homogeneous and heterogeneous radiation. Homogeneous radiation (high voltage) means the use of a bundle of rays of one particular penetration. Heterogeneous (low voltage) means the use of a large number of rays of all penetrations, filtering out those rays likely to injure the skin. It is important that the heterogeneous radiation be utilized. It has its limitations, but the newer method should be an addition and not a substitute. Radiation does not destroy or remove unwanted cells like the cautery or knife. Profound changes are set up, which allow them to be absorbed or replaced by healthy cells. This is important, for it means that malignant cells can be made to undergo a change, resulting in their replacement by normal tissues without necrosis taking place—in short a metamorphosis without cellular death. It is thus evident that there is a local indirect effect of radiation. Carried further is it not possible to create it on a larger scale generally, calling up all nature's forces to assist in the cure? The work of many physicists supports this theory.

The Relative Merits of the Various Treatments of Peptic Ulcer.—BALFOUR (*Minn. Med.*, 1925, **8**, 218) believes that the methods which are worthy of discussion include both medical and surgical procedures. The surgical procedures of unquestioned merit are excision alone, excision with gastroduodenostomy, gastroenterostomy with or without excision and partial gastrectomy. The indications for medical treatment depend largely on the situation of the lesion. In chronic gastric ulcer prolonged medical treatment is justified only when surgery is absolutely contraindicated, because of the age or the condition of the patient. The more familiar one becomes with the uninterrupted course of chronic gastric ulcer, which is one of progressive disability, the more certain one becomes of the fact that prolonged medical treatment is never justified if the patient is fit for operation. In cases of chronic duodenal ulcer, such serious objections to medical treatment do not exist since the symptoms are usually not so severe, the disability so great, nor the danger of fatal complications so marked as in cases of gastric ulcer. It is generally recognized that the fundamental principle in the successful treatment of gastric ulcer is the removal of the ulcer whenever feasible. For small accessible ulcers, local excision by cautery or knife, combined with gastroenterostomy gives excellent immediate and late results and the procedure is usually safe and simple. For larger ulcers partial gastrectomy is the operation of choice since it cannot be determined whether or not such ulcers are malignant and it is well established that all chronic gastric ulcers are potentially malignant. In the surgical treatment of chronic duodenal ulcers, one fact stands out that no one operation will give perfect results. Four procedures are considered in the article: Gastroenterostomy, with or without excision of the ulcer, pyloroplasty or gastroduodenostomy with or without excision, excision alone and partial gastrectomy. To attain the best results from gastroenterostomy a safe principle to follow is that the more extensive the lesion, the more definite the indication.

PEDIATRICS

UNDER THE CHARGE OF
THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Mumps of the Pancreas.—STEVENS (*Arch. Pediat.*, 1925, **42**, 333) reports 4 cases of mumps involving the pancreas. An analysis of his cases showed that all 4 were in boys, and their ages ranged from six to almost thirteen years. The onset was rather sudden, after doing well, on the fifth or sixth day of the infection. The first symptom noted was rising temperature. The fever rose from nearly normal to 102° or more and was sustained at the high level for the period of active symptoms, which lasted from one and a half to two and a half days. The highest recorded temperature was 104°. The pulse was rapid and proportionate to the temperature. Pain was generally of mild character at the onset, and was referred to a point just below the ensiform. It was described as of a steady, aching character. Abdominal cramps in 2 cases may have been caused by liberal catharsis given at home to cure the pain. Tenderness in the epigastrium was a constant sign. Pressure to elicit this sign usually brought on a wave of intense nausea. It was not possible to make out the presence of a mass with any certainty. This tenderness in the epigastrium persisted for several days after the temperature returned to normal. Vomiting was an outstanding symptom, coming on within a few hours and persisting for two days with total intolerance for food. Half of the cases could retain sips of water only. In the more severe cases the repeated retching brought up bile-stained fluid on the second day. The prostration was out of proportion to the degree of pain complained of. There was no true shock, although general weakness is to be expected after continued vomiting. Constipation was the rule. The shortest period of active symptoms was a day and a half and the longest period was two and a half days. The condition terminated by a rapid fall of the temperature to normal and with a cessation of nausea. There were two inconstant symptoms. Icterus of a mild grade was noted in 2 cases. This may have been secondary to the bilious vomit and reabsorption. In another case conjunctival hemorrhages occurred, presumably from the severe retching. The author thinks that this condition is a metastasis to the pancreas of the virus causing mumps. He feels that the great danger lies in wrongly diagnosing this condition as an acute surgical process. He thinks that the symptoms are very suggestive of appendicitis, intussception and ileus. In the presence of a parotitis the diagnosis lies in favor of the pancreatic mumps.

Difficulties in Diagnosis of Acute Phase of Epidemic Encephalitis in Children.—HALLIDAY (*Lancet*, 1925, **1**, 763) points out that the diseases most liable to be confused are gastroenteritis, tuberculous meningitis and pneumonia. He emphasizes the fact that examination

of the cerebrospinal fluid will always exclude meningitis, and in certain instances will establish a diagnosis of encephalitis. In gastroenteritis the gastrointestinal symptoms are often overlooked on account of others suggesting a disease of the nervous system, such as headache, delirium, drowsiness, sighing respirations and pseudoptosis. Pneumonia in its early stages before the development of physical signs in the chest may be mistaken for encephalitis when it is ushered in by convulsions, delirium, twitchings, meningism, drowsiness, vomiting and pain in the side. On the other hand, pain in the side, a cough and rapid respirations may be the first symptoms of encephalitis.

Congenital Cardiac Defect in Children.—MACGREGOR (*Edinburgh Med. Jour.*, 1925, **32**, 251) reports an interesting case which showed some unusual features. There was an absence of the right auriculoventricular orifice. There were also defects in the interauricular and interventricular septa. The heart was greatly enlarged. Both atria were markedly dilated and communicated freely with each other through the foramen ovale which was widely patent. There was no communications between the right atrium and the right ventricle, the right auriculoventricular orifice and the tricuspid valve being entirely absent. There was thus no outlet for blood from the right atrium except through the foramen ovale. The pulmonary artery arose from it in the usual position, and it possessed a perfectly normal valve, and was of the usual caliber. The left auriculoventricular orifice was somewhat wider than usual, but was in the natural position, and possessed a valve with two cusps, exactly resembling a normal mitral valve. The aorta was normal in every way as was also its valve. The ductus arteriosus was patent, but very narrow and seemed to be in the process of becoming obliterated. In the interventricular septum there were two apertures. The larger, which readily admitted the forefinger, was situated in the upper part of the septum, immediately below the aortic valve, and communicated with the infundibular portion of the right ventricle. The other, which was barely half as large, was situated near the apex, the two openings being separated from each other by a thick band of muscular substance. No cardiac defect was suspected in this case until the day of death, which occurred when the patient was seven weeks of age.

Pneumonia in Children.—ENGEL (*Berlin. klin. Wchnschr.*, 1925, **4**, 681) found invariably in the paravertebral lobular pneumonia of infants a tendency for the posterior portion of the right upper lobe, and to a less extent of the center of the lower lobe to become involved. This seems to be due to a relative atelectasis of these parts. The chest of an infant is not capable of much distention, and is practically in the inspiration position. The air can be increased, therefore, only by tachypnea, not by deeper respiration. The imprints of the ribs, or the intercostal bulgings of the lungs, were quite pronounced in infants that were dyspneic. This phenomenon and the typical localization of the pneumonia becomes rarer after the first year. The diffuse lobular pneumonia in infants causes surprisingly slight physical symptoms in spite of the gravity of the condition. Lobar pneumonia affected the right upper lobe in 27 and the left lower lobe in 3 of the

30 cases less than twelve months of age. This tendency is evident in the first three years of life. It may be due partly to the same mechanical factors which cause the localization of the paravertebral dystelectatic pneumonia. The left upper lobe that usually remains free has its regional lymph nodes outside of the lungs, in the mediastinum along Botalli's duct and the arch of the aorta, and not in the hilum. The summer peak of mortality of children from gastrointestinal diseases has been superseded by the winter and spring peak from respiratory infections. Scarlet fever and diphtheria kill fewer children than the pneumonia complicating measles and whooping cough.

Tetany as a Cause of Convulsions in Very Young Infants.—POWERS (*Jour. Am. Med. Assn.*, 1925, **84**, 1907) reports a case. When first seen a number of possibilities were suggested and considered. Many of these were eliminated or considered as highly improbable on general clinical grounds. Of this number infantile tetany was one. This proved to be the correct diagnosis. It was strongly suggested by the electrical reactions, but was definitely established by the finding of the blood calcium concentration of 5.93 mg. per 100 cc of serum. The highly favorable response to treatment with calcium chlorid, cod-liver oil and direct sunlight would offer confirmation of the diagnosis. Several points in the history and symptomatology presented by the infant were in evidence against the diagnosis of infantile tetany. Until the electrical reactions were determined there was no point in favor of this diagnosis. The history gave a statement of a prolonged labor with face presentation, and this was highly suggestive of a birth hemorrhage as the cause of the convulsions. The convulsions were largely limited to the right side. While the convulsions attributed to birth injury may be and usually are generalized, the presence of predominantly unilateral attacks were especially suggestive of an injury in the nature of a cerebral hemorrhage. The patient showed none of the characteristic symptoms and signs of tetany. There was no laryngeal spasm, no tenseness of the facial muscles, no Chvostek's sign and no carpopedal spasm. While local twitchings occur frequently in manifest tetany, frank convulsions are rarely predominantly unilateral as in this case. The fact that as demonstrated by this case the only clinical manifestation of tetany may be convulsions should be borne in mind. Another point to be remembered is that tetany may develop in a very young infant, this patient being only five weeks of age when the symptoms were manifested. Another point is the possibility of congenital tetany just as there is a possibility for congenital rickets.

The Heart in Diphtheria.—MARVIN (*Am. Jour. Dis. Child.*, 1925, **29**, 433) made an electrocardiographic and clinical study of 90 patients with diphtheria. The only abnormalities in the electrocardiographs were disturbances in the auriculoventricular or the intraventricular conduction. Sinus arrythmia occurred invariably in young patients with heart rates below 95 per cent. Auricular and ventricular premature beats, sinoauricular block and variations in the form of the *P*-wave were noted seldom and appeared to have no significance. No evidence was obtained to indicate that in some patients the heart was primarily injured and in some others the peripheral circulation suf-

fered the first and greatest damage. In patients with circulatory impairment the picture seemed to be that of myocardial failure. The signs of myocardial involvement which appeared to be of the greatest value were vomiting, hepatic engorgement and a change in the first heart sound. Syncope occurred but once and gallop rhythm was noted only three times. There was a complaint of abdominal pain in 5 of the 13 fatal cases. Necropsy in 5 cases revealed widespread myocarditis. In 1 case the entire conduction system was profoundly damaged, in 1 the sinoauricular node was alone affected and in the others the conduction system seemed normal. The vagus nerves were found to be normal in the 1 case in which an examination was made. The electrocardiographs prove of great value in diagnosis and prognosis.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

The Use of Radium in Uterine Cancer.—At present radium is little used in the treatment of cancer of the uterine fundus because the results of operation in this disease have been quite satisfactory. GRAVES (*Am. Jour. Obst. and Gynec.*, 1925, **9**, 445) goes a bit further and warns that carcinoma of the fundus is a distinct contraindication to the use of radium because he has shown that early cancer of the fundus that is entirely curable by operation is liable to recur when treated by radium alone. This uncertain curability by radium is sufficient to condemn its use, but there is still another reason which should convince the most enthusiastic of radiologists. It has long been a matter of observation that cancer of the fundus metastasizes first in the ovaries. The mode of transmission of the disease from the endometrium to the inner tissues of the ovary was a scientific mystery until the epochal work of Sampson taught us the frequency with which endometrial elements may become transplanted into the ovarian substance. The intrauterine application of radium will not destroy endometrial elements in the ovaries, so that the treatment of cancer of the fundus should be by radical operation that includes both ovaries. In regard to *cancer of the cervix*, the author reminds us that before the advent of radium the extended Wertheim operation had reached the limit of its possibilities and progress depended solely on the improvement in skill of the individual operator. Radium has given new hope in treating this dreadful and rapidly increasing disease. In its use as a palliative, the author believes that there is almost no case so far advanced in which the distressing discharges and often the pain may

not be alleviated by irradiation. In less advanced but still incurable cases the disease may, with few exceptions, be checked by a single treatment, so that the patient may live from one to four years in perfect health. When recurrence does take place it is apt to be internal and unassociated with the offensive discharges and fistulæ that were formerly universal in the final stages. Though not a few surgeons have discarded operation altogether in the treatment of *operable* cervical cancer in favor of radium, he has not yet come to a final conclusion. At first convinced that it was the duty of the surgeon to operate upon every operable case instead of taking the more comfortable path of irradiation, he has latterly made certain concessions to the radiologists. For example, he has greatly modified his classification of cases. He has changed the term "operability" to "curability by operation," which has quite a different significance. Whereas formerly over a period of many years in the author's clinic they operated upon about 60 per cent of all cases, they now subject to operation only about 20 per cent. During the last five or six years they have carried on parallel series of operated and irradiated cases, in which the disease is limited to the cervix and frankly curable either by operation or radium. Such patients have been chosen for irradiation as, on account of obesity or constitutional weaknesses, incurred a special risk in operation. Sufficient time has not elapsed to draw authoritative conclusions from this series, especially as the operated cases greatly exceed the others in number. Nevertheless a recent comparison of the two types of cases of less than five years' duration shows a similarity of results that has been surprising to the author and encouragingly favorable to the use of radium.

Movable Kidney.—In summarizing his experiences in the treatment of movable kidney, MATHÉ (*Surg., Gynec. and Obst.*, 1925, **40**, 605) states that the great majority of movable kidneys cause no symptoms and require no treatment. In a certain percentage of cases, however, renal mobility forms a definite clinical entity characterized by lumbar pain, urinary, gastrointestinal and nervous disturbances, loss of weight, etc., and requires fixation by abdominal support or surgical intervention. The condition is more common in the female because the renal fossæ are shallower, cylindrical or even funnel-shaped, being wider below than above. This predisposition to displacement is increased at puberty because of the widening of the bony pelvis. Its greater frequency on the right side is due to the shape of the renal fossa, the presence of the liver on that side and the weaker support afforded by the less well-developed right perirenal fascia. The majority of cases of renal ptosis can be relieved by the proper abdominal support, fattening and strengthening exercises. On the other hand, Mathé says that nephropexy is a justifiable operation. It has been employed by numerous urologists of note who have found it satisfactory. It relieves symptoms and is indicated in the following cases of movable kidney: (*a*) When the belt fails or is poorly tolerated; (*b*) in those cases complicated by ureteral kink caused by fibrous bands; (*c*) when the sag of the kidney has caused the ureter to kink over an aberrant vessel; (*d*) in those cases in which adhesions have developed around a prolapsed kidney holding it in place; (*e*) in chronic colon pyelitis when faulty

drainage due to increased mobility is not corrected by the belt. He has employed nephropexy with success in 96 per cent of the 30 cases operated on. Of those 46 per cent had obtained no relief from mechanical supports. He believes that surgical suspension of the kidney has fallen into disrepute not on account of its inefficacy, but because it has been performed when it has not been indicated, the technic has been faulty or there has been failure to realize the necessity of exposing the ureter and relieving any condition which might be present, which unrelieved, would defeat the purpose of the operation.

Blood-sedimentation Test.—According to the experiences of BAER and REIS (*Surg., Gynec. and Obst.*, 1925, **40**, 691), the blood-sedimentation test is useful in determining the presence or absence of infection in the body. With pelvic pathology a negative sedimentation test (a sedimentation time over two hours) conclusively rules out pelvic infection. The rate of sedimentation is directly proportional to the virulence of the infection and the test is a further aid in determining the safe time for operation in cases of pelvic inflammatory disease, and they believe that this test seems a more delicate prognostic index, good or bad, than either the leukocyte or temperature curve. The sedimentation time, or rate, is the number of minutes required for the red blood cells to separate from the plasma of citrated blood. Many methods and types of tubes for making such determinations have been devised. The technic of Linzenmeier appears to the authors to be the most reliable, the most accurate and also the simplest of all methods that have been suggested, and it was therefore used by them in this study. The tubes used are of hard glass, 5 mm. in diameter and 6.5 cm. in length and have a capacity of more than 1 cc. They are marked at the 1-cc point and also at 6, 12, 18 and 24 mm. below this mark. The tubes as well as the syringe with which the blood is drawn from one of the superficial veins at the elbow, must be perfectly clean and dry. Two-tenths cubic centimeter of a 5 per cent sodium citrate solution is drawn into the syringe and then 0.8 cc of blood. This is shaken until mixed and then placed in one of the tubes and allowed to stand at room temperature. The blood mixture level must be exactly at the 1-cc mark. The time is taken when the mixture is placed in the tube and again when the line of demarcation between the erythrocytes and the plasma reaches the 18-mm. mark; a millimeter reading is also taken at the end of one hour. This latter reading has been recently recommended as being more comparable than the number of minutes required for the line of demarcation to reach the 18-mm. mark and besides much time can be saved in specimens requiring several hours for complete sedimentation. The sodium citrate solution must be comparatively fresh and the tubes must be kept vertical, for slanting the tubes increases the rate appreciably. If the blood clots before being well mixed with the citrate solution the test is valueless. There are many theories to explain the reason for this blood phenomenon but no definite conclusions have been reached.

Ectopic Muellerianoma.—In a certain percentage of women the process of menstruation is abnormal, inasmuch as part of the menstrual blood finds its way into the Fallopian tubes and escapes into the pelvic

cavity, carrying with it either endometrial epithelium and stroma cells or Fallopian tube epithelium. These elements are deposited upon the surfaces of the various pelvic organs, and in a certain percentage of instances become embedded and grow into them. They proliferate actively and menstruate concurrently with the uterine endometrium. Our knowledge of this subject is largely due to the original work of Sampson which we have repeatedly quoted in the past. This subject has attracted the attention of BAILEY (*Jour. Obst. and Gynec., Brit. Emp.*, 1924, **31**, 539), who has presented a rather extensive review of the life history of these "chocolate" cysts. He states that misplaced Fallopian tube epithelium also reacts definitely to menstruation, but in a lesser degree than uterine epithelium and it is less invasive than the endometrial cells. These abnormally situated epithelial elements penetrate into the tissues of the affected organs—the ovary apparently being best suited for their activities—and eventually produce in them tumor formations and excavated cavities containing the products of their menstrual activity. Many names have been applied to these tumors, such as ovarian hematoma, ectopic adenoma, adenomyoma and endometrioma, but no one of these names can thoroughly embrace both the endometrial and Fallopian tube types of this extrauterine pelvic tumor, and therefore the author suggests the name of "ectopic muellerianoma," which is expressive of both types of the disease, since the abnormally situated elements in each case are of Muellerian origin. These tumors are only locally malignant and do not tend to form metastases.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

DEWAYNE G. RICHEY, B.S., M.D.,

MERCY HOSPITAL, PITTSBURGH, PA.

Further Statistics on Chlorin Gas as a Treatment for Respiratory Diseases.—JONES AND GAROFALO (*Arch. Otolaryngol.*, 1925, **1**, 58) reported the results of about 800 chlorin-gas treatments administered to 220 individuals, suffering from acute, subacute and chronic inflammatory processes of the respiratory tract, hay fever, asthma or suspected tuberculosis. The technic of treatment and the dilution of the chlorin gas used (0.02 mg. per liter) was that recommended by Vedder and Sawyer in their original report (*Jour. Am. Med. Assn.*, 1924, **82**, 764) of the chlorin treatment. Treatments were given only once in some instances and in others were repeated at intervals of twenty-four hours for several days. There was an improvement in the acute cases involving the upper respiratory tract, as indicated by shrinking of the mucous membrane, diminution of discharge, relief of irritation and freer breathing—all of which beginning immediately after the treatment but lasting only a few hours. Extension of the inflammation into the lungs and trachea was not perceptibly influenced.

The authors state that in "Asthmatic patients, allergic and tuberculous patients chlorin treatment is contraindicated." The chlorinated air did not alleviate freely suppurative conditions of the rhinopharynx. Although their number of cases was small, it was felt that whooping cough did not respond to the treatment. In the dilution tolerated chlorin was not sufficiently germicidal to act as a sterilizing agent for operations on the nose and throat. In 106 treatments, where the bacteriologic findings were compared with the clinical results, there was an agreement in 67 cases (65.1 per cent) and disagreement in 39 cases 34.9 per cent).

Bacteriologic Study of the Nasopharynx in Patients Treated with Chlorin Inhalations.—In a companion article, PATTERSON (*Arch. Otolaryngol.*, 1925, **1**, 64) gave the findings of bacteriologic studies of the nasopharynx on the same individuals treated with chlorin gas inhalations. The technic consisted in culturing the nasopharynx by means of the West tube and planting on rabbits' blood-agar plates. The cultures were taken before entering the chlorin room and five minutes after the treatment had terminated. At the end of twenty-four hours' incubation the number of colonies of those plates seeded from the persons before treatment was compared with those after treatment. The colonies, as observed forty-eight hours after inoculation, were classified as green, hemolytic, staphylococcus-like and diphtheroid. In a total number of 184 tests the growth on the after-treatment plate was less in eighty-eight instances, or 48 per cent of the total. In 43 instances, or 24 per cent, the after treatment plate showed more growth than the control. In 53 instances, or 28 per cent, there was no obvious difference. Of the various types of microörganisms the author felt that the results indicated that hemolytic streptococci and diphtheroid bacilli were affected most. Blood-agar plates inoculated with pure cultures of some common pharyngeal bacteria, and then exposed in an atmosphere containing 0.015 mg. chlorin per liter for various intervals up to one hundred and twenty minutes, showed very little or no effect of the gas on the subsequent development of the bacteria, except in plates exposed for more than ninety minutes. A chlorin concentration of 0.02 mg. per liter of air gave a distinctly more appreciable reduction in the bacteria of the nasopharyngeal mucus in the patients, and exhibited a greater inhibitory effect on the plate cultures. The bacteria suspended in the air itself appeared to be very largely destroyed by the chlorin. From her investigations the author concludes that "Sterilization of the respiratory mucous membrane by inhaltion of chlorin in a concentration of 0.015 to 0.02 mg. per liter of air for an hour or two is not to be expected;" that "The concentrations of chlorin used do exert an effect, however, and often this may be in the direction of microbe reduction, of possible assistance to the body defenses in combating superficial infection;" and that "Although chlorin inhalation is not without possibility of injury, its extensive application to acute superficial respiratory inflammations, under suitable scientific control, appears justified in the light of the laboratory studies. The ultimate decision as to its value must be based on extensive clinical trial."

Value of Chlorin in the Treatment of Colds.—Realizing the importance of controlled observations, DIEHL (*Jour. Am. Med. Assn.*, 1925, **84**, 1629) subjected 425 university students to chlorin gas in a concentration of from 0.015 to 0.0175 mg., and compared the results with those observed on 392 students who received medical treatment for their acute respiratory diseases. By means of a questionnaire, sent to the patients at the end of a week, the results of the chlorin inhalations were ascertained. Of the total that were treated with chlorin, 51.4 per cent reported themselves cured within three days, while 47.9 per cent of those given medical treatment recovered in the same time, showing practically no difference. There was still less difference between the percentages that recovered under chlorin and medical treatments during the first week, 73.3 and 72.6 per cent, respectively. However, the percentage of cures within the first day was consistently higher with chlorin than with medical treatment. This difference was most marked when the colds were treated within the first three days, but the percentage of cures with chlorin was also higher for colds treated after the third day and for the total number treated. The beneficial effects of chlorin evidently were experienced within the first day after the treatment, because each day after the first the percentage of recoveries was higher from medical treatment than from chlorin. The chlorin treatment was apparently more beneficial in acute rhinitis than in any other type of acute cold. The author confirms the observations of others that persons subject to asthma suffered ill effects from the chlorin inhalations. The results of the treatment of whooping cough were somewhat encouraging, but not conclusive.

New Method of Demonstrating the Labyrinth of the Inner Ear in Situ.—After a macerated temporal bone has been thoroughly cleaned, degreased, bleached and dried, the empty spaces of the labyrinth, seventh nerve and mastoid cells, etc., were filled with Wood's metal through the internal auditory meatus, according to Siebenmann's method. FREEDMAN (*Bull. Internat. Assn., Med. Museum*, 1925, **11**, 33) then decalcified the superficial bony tissue by immersing in a solution of 5 per cent nitric acid for about two days. When the temporal bone was sufficiently decalcified, so as to render cutting it with a scalpel easy, the superior semicircular canal was denuded. By following the posterior limb backward the posterior semicircular canal, embedded in the posterior part and running parallel with the posterior surface of the petrous portion of the temporal bone, was encountered. By drilling in the enclosed angle between the superior and posterior canals the horizontal canal was found. Lateral to the arch of the horizontal canal occurred the antrum filled with Wood's metal, which was whittled away, exposing the arch of the horizontal canal and the horizontal portion of the facial nerve beneath it. With very little dissection through the external auditory meatus the cap of bone of the promontory was lifted up, exposing the rounded basal turn of the cochlea. Removal of the roof and anterior surface of the internal auditory meatus brought to light the seventh and eighth nerves. The white metallic semicircular canals and cochlea were painted green and the nerves the conventional yellow. The author concludes that "A temporal bone prepared in this fashion in conjunction with

the corrosion method of Siebenmann, and the usual method of exposing the hollow semicircular canals and cochlea in the dry bone, form an almost indispensable 'triad' for the proper orientation of the labyrinth of the inner ear and its relation to the seventh nerve, both for the student and ear specialist."

RADIOLOGY

UNDER THE CHARGE OF

RUSSELL D. CARMAN, M.D.,

HEAD OF THE SECTION OF ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINN.

The Differential Diagnosis of Certain Chronic Lung Lesions.—In roentgenologic diagnosis of lung lesions, accuracy depends upon the interpreter's knowledge of the lung anatomy and pathology, according to FRANK S. BISSELL (*Am. Jour. Roentgenol. and Rad. Ther.*, 1925, **13**, 2). Tuberculosis is most commonly an aërogenic infection and its earliest lesions occur in the area of Chauvet, and also anteriorly in the second and third interspaces near the periphery. A healed and an active lesion may exist in opposite lungs; primary basal tuberculosis is very rare, and its differential diagnosis cannot be made roentgenologically. Tuberculous pleurisy is almost always associated with tuberculosis of the lung. It is usually possible to make a roentgenologic differentiation between a cavity and a simple abscess by searching other parts of the lung fields for the more characteristic evidence of tuberculosis. In tuberculous infection there is a marked tendency to early involvement of the lung parenchyma, often restricted for the time to one or more primary lobules, taking on a pyramidal shape with the base toward the periphery, and is usually in the upper-lung fields. In the chronic bronchopneumonia of streptococcic origin the process is almost invariably unilateral and usually confined to one of the lower lobes.

Final Results in the Treatment of Carcinoma of the Uterine Cervix at Radiumhemmet, Stockholm.—In a report on 505 cases of primarily radium treated carcinoma of the cervix, within the period 1914–1921, JAMES HEYMAN (*Am. Jour. Roentgenol. and Rad. Ther.*, 1925, **13**, 2) demonstrates very encouraging results. The technic used, as elaborated by Forssell, is a small number (usually 3) of intensive treatments (each 105 to 112 mg. radium element) with strong filtration (equivalent to 3 to 4 mm. lead), given in the course of three to four weeks. At first only inoperable cases were treated, but following a report in 1919–1920 by the author that 33.3 per cent of his cases were alive four to five years after treatment of inoperable cases, operable cases were also sent to the "Radiumhemmet." Of 505 cases, one-third were forty-five years of age or less, one-third forty-six to fifty-five years and one-third over fifty-six years of age. In 217 cases treated, 20.29 per cent were symptom free five years after the commencement of treatment. The

author has noted that any variation from a definite plan of treatment affects the end result; that repeated removal of tissue during treatment is very dangerous; that the average result of radium treatment on operable and borderline cases is on a par or better than results obtained by surgery; that the primary mortality is very small with radium; that this treatment has great developmental possibilities; and that for uniform results a very exacting technic should be followed closely.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.,

PROFESSOR OF PSYCHIATRY AT UNIVERSITY OF COLORADO, DENVER, COLORADO.

The Present Status of the Malarial Inoculation Treatment for General Paresis.—Since Wagner V. Jauregg introduced the malarial inoculation treatment of paretic neurosyphilis much work has been done in different countries and many favorable results have been reported. In this article LEWIS (*Jour. Nerv. and Ment. Dis.*, 1925, **61**) reports the results obtained in the treatment of 68 patients at St. Elizabeth's Hospital, Washington. Nine patients failed to develop malaria and 8 of those who did respond could not be followed up because they left the hospital. In 16 patients "complete remissions" occurred. In 19 others the disease was arrested. Twelve progressed to extreme deterioration and 13 died either during or shortly after treatment. The author discusses the following points: (1) In the selection of cases paresis must be diagnosed and differentiated by at least two of three objectives (mental, physical and serologic) one of which must be the serologic picture. The vascular type of neurosyphilis should be ruled out. (2) Some of the most notable remissions have occurred in late cases in which syphilitic aortitis was perhaps present. (3) Written permission for the treatment should be obtained as it is not without some danger. (4) The absence of quinin idiosyncracy should be determined before treatment is begun. (5) Malarial blood must be kept at 37° C., and must not be shaken lest the plasmodia perish. (6) Intramuscular injection is as good as the intravenous method. The blood must show only the pure tertian type of malaria. (7) Inoculation malaria responds well to quinin treatment. (8) Many paretics do not develop malaria upon inoculation. (9) Malaria itself probably is a factor in certain deaths occurring with this treatment. (10) Muhlen's scheme of treatment gives the best results in the interruption of the malaria. (11) Reviewing the results of a number of investigators the author considers these to depend essentially upon the stage of the disease, the earlier the more certain the remission. The maximum results are not obtained at once. Permanency of improvement cannot be determined until sufficient time has elapsed. (12) Reese and Peter's observations on blood and spinal fluid, particularly in that there is no

parallelism between clinical improvement and spinal fluid changes, are confirmed. (13) Objective improvements are striking. (14) Regarding the beneficial action of malaria the author believes: (*a*) There can be no specific reaction; (*b*) the rise in temperature is not alone responsible; (*c*) Mueller's concept of a vasodilation in the brain should be seriously considered. Changes in vascular tonus occur in various parts of the body following injection. The abdominal vasodilation is quickly neutralized by the unimpaired vasoconstrictors but the same dilation in the local inflammatory areas in the brain is of longer standing. If this should be found to be true a follow-up specific therapy is perhaps indicated. The results obtained are strikingly better than those gained by any other method. A conscientious investigation of the phenomenon produced is indicated.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ., M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO; TORONTO, CANADA,

AND

W. L. HOLMAN, M.D.,

ASSISTANT PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

The Differentiation of the Paratyphoid-enteritidis Group—With a view to obtaining some conception of host specialization of paratyphoid-enteritidis bacilli from mammalian sources (other than human) an exhaustive study has been made by EDWIN O. JORDAN (*Jour. Infect. Dis.*, 1925, **36**, 309). The report consists of a thorough review of the existing data and an examination of over one hundred strains of paratyphoid-enteritidis bacilli from widely distributed sources. In connection with the former, exact classification is difficult by reason of incomplete observations of strains in numerous instances by those reporting them. Confusion in classification has arisen because certain German writers insist on classing B. paratyphosus B with B. suipestifer, while English bacteriologists identify B. suipestifer with the so-called Aertrycke strains. The author concludes that B. paratyphosus A is apparently an exclusively human strain. He has found no authentic instance recorded of natural animal infection with this type. In the horse a specialized member of the group, B. abortivo-equinus, predominates, and he believes it to be the only organism in the group producing natural infection in equines. It is serologically distinct from all other members of the group. Culturally it may be distinguished by the following characteristics: (1) B. paratyphosus B shows rapid arabinose fermentation, rapid dulcitol fermentation, trehalose fermentation, while (2) B. suipestifer shows no blackening lead acetate, no inosite fermentation. This strain has never been found in infections of other animals. In rodents (chiefly mice, rats, guinea pigs and rabbits) two types are found: B. enteritidis, most commonly

in laboratory rats (sometimes in mice); the other type in rodents, particularly guinea pigs, is the B. paratyphosus B. aertrycke type. The proportion of the two is not known. In pigs 38 out of 50 cultures were culturally and serologically of the B. suipestifer type. The only other strain of this type of animal origin was from a monkey. No strain has been encountered from rodent or bovine sources. On the remaining 12 of the 50 strains 10 were B. paratyphosus B, all true Schottmüller, and two other types have been found in swine, B. enteritidis and B. voldagsen (B. paratyphosus C?). Bovine strains are usually B. enteritidis or B. paratyphosus B, aertrycke type. The few sheep strains studied are all B. paratyphosus B, aertrycke type. Thus it will be seen that host specialization has occurred to a considerable extent in man (B. paratyphosus A), horse (B. abortivo-equinus) and pig (B. suipestifer). The relation of B. paratyphosus B, aertrycke, to rodents is not so marked. B. paratyphosus B (Shottmüller) is found in human paratyphoid fever almost as often as B. paratyphosus A, but unlike the latter it is also found in swine. The most cosmopolitan member of the group is B. enteritidis, found in human, porcine, bovine and rodent infections.

"Hormone" Medium.—A modification of Huntoon's "hormone" media is described by BAILEY (*Jour. Infect. Dis.*, 1925, **36**, 340). The author claims that the media retains all the qualities of other "hormone" media, with the added advantages of being clearer, less expensive and even richer in "hormone" content than the others. The egg is omitted as being unnecessary for purposes of filtration, and it is suggested that it may even be a source of stubborn contamination. Special reference is made to the preparation of "hormone" blood agar and its value for preserving pneumococci and streptococci. Sixty-two out of 68 cultures of pneumococcus and all of 32 cultures of streptococcus were kept alive on this medium for twelve months without transplantations.

Phagocytosis of Erythrocytes in the Bone Marrow with Special Reference to Pernicious Anemia.—PEABODY and BROUN (*Am. Jour. Path.*, 1925, **1**, 169) precede a report of an investigation of the phagocytosis of red blood cells in the bone marrow by clasmatocytes (Sabin) with a survey of the present knowledge of this subject. For control observations 4 specimens were studied of normal vertebral bone marrow (from patients dying from trauma) and 130 specimens of vertebral bone marrow from patients dying as a result of a great variety of conditions. The basis of the paper is a study of 11 cases of pernicious anemia, 10 of which died during an acute phase of the disease and 1 during a remission. Excellent results were obtained for study by fixing the smears from the bone marrow or from emulsions of bone marrow in salt solution, in Zenker's solution, and then staining. The stains used were eosin and methylene blue or one of the Romanowsky stains. Neutral red and Janus green are also recommended. They conclude that phagocytosis of erythrocytes occurs to a very limited extent in normal marrow, though it may be considerably increased by a variety of pathological conditions, notable among which are certain cases of cirrhosis of the liver and of infectious diseases, such as pneumonia, typhoid fever and tuberculosis. On the other hand, in the

active stages of pernicious anemia it occurs to a degree which, with rare exceptions, is not met with in other diseases, and during a remission it may cease to be a prominent factor in the bone marrow. The ingested cells, furthermore, do not appear to be foreign cells that have been introduced by transfusion. Views are presented on the reason and process of the phagocytosis and on whether or not it is an incident in the disease or a significant phase in its pathology. It is suggested that phagocytosis of erythrocytes may be a factor in the production of the hemolytic jaundice and of the anemia in pernicious anemia.

The Combined Microscopic Demonstration of Glycogen and Lipoids.—The demonstration of glycogen and lipoids in the same preparation offers difficulty because these two substances possess very different solubilities. The method which has previously been in use, and has been modified by various authors, consists of a combination of the best carmine staining along with the use of osmic acid. This method has not been entirely satisfactory inasmuch as the osmic acid treatment leads to variable results, and the reduction of osmic acid is brought about mainly by oleic acid while the remaining fatty substances are unaffected. ARNDT (*Centralbl. f. allg. Path.*, 1925, **35**, 545) suggests using a 10 per cent solution of formalin saturated with dextrose for the fixation of the specimens. The material is then cut on the freezing microtome and subsequently handled either in saturated solutions of dextrose or in 70 per cent alcohol. The author made use of solutions of chlorophyl for the staining of the fatty substances, hematoxylin for the staining of the nuclei and levulose for the mounting of the sections. The regular Best method for staining glycogen was found satisfactory. He claims to have been able to obtain very good results for the dual demonstration of fat and glycogen, and states that the method is important for the study of the tissue changes which arise when these two substances make their appearance in different organs in disease. In certain tissues he was able to demonstrate the presence of both of these substances within the same cell.

Primary Tumors of the Ureter.—Primary tumors of the ureters are quite unusual. The most common variety that has been found is the one arising from the epithelial lining of the tube and resembling a tumor similar in origin to that found in the pelvis of the kidney. A few cases of mixed tumor have also appeared in the literature and the still rare tumors of smooth muscle origin have been described. DJENG-YAN KU (*Centralbl. f. allg. Path.*, 1925, **35**, 549) reports a case of myosarcoma arising in a man, aged seventy-five years, which had been growing slowly until it involved the entire circumference of the lower portion of the ureter and then spread into the surrounding tissues. This tumor, late in its development, brought about a constriction of the ureter with a secondary hydronephrosis. The author was able to determine that the tumor was composed of muscle tissue containing numerous giant cells. The tumor was intimately attached to the muscle layer of the ureter and, although its malignant qualities were not evident in all its portions, it showed active mitoses in certain parts and an invasive quality in the neighboring structures. The neighbor-

ing connective tissues showed a peculiar hyalin degeneration not unlike amyloid. The author suggests that the tumor is of congenital origin, inasmuch as he also found multiple lipomata in the neighborhood of the tumor and bone formation in both lungs.

Variations in Specificity and Virulence of Pneumococci during Growth in Vitro.—Using a strain of Type I pneumococcus, REIMANN (*Jour. Exper. Med.*, 1925, **61**, 587) has studied the variations induced in the organism by growth in artificial media, and has attempted to correlate these differences. Plain bouillon was used as a medium, to which were added varying concentrations of bile or homologous or heterologous immune serum. The bacteria were adapted by successive transfers to the presence of the bile in the medium. Blood agar was used for detecting colony differences, and the test for the immunological specificity was made by the so-called thread reaction. In certain cases it was found advisable to work with single cells, an interesting method for the isolation of which is reported. After the culture had been transferred 240 times in broth observations were made. Colonies were found to resolve themselves into rough (R) and smooth (S). The S strain remained type specific for Type I serum, but the R strain clumped in all three sera. Furthermore the S strain produced a specific soluble substance for the precipitin reaction while the R failed to do so. Similarly the S strain retained its virulence for white mice while the R did not do so. Both strains coagulated milk and fermented inulin and only the S strain showed a capsule. Growth in bile media produced similar changes, successive transfers finally eliminating the S strain. The same findings resulted from using a medium containing 1 per cent Type I antipneumococcus serum. Animal passage eliminated the R forms. S and R forms could be separated by growing the bacteria in heterologous serum. The work throughout indicated that the S form can be readily changed to the R, but that the reverse change is not probable, the whole trend of pneumococcus cultures being toward a decrease in virulence and a loss of type specificity. The changes in individual bacteria appear to be abrupt. Clearly written details of the experiments are given.

Experimental Pneumonia in Mice following the Inhalation of Streptococcus Hemolyticus and of Friedländer's Bacillus.—STILLMAN and BRANCH (*Jour. Exper. Med.*, 1925, **41**, 623) report a study of a series of mice exposed to fine bacterial mists of pneumococcus, Streptococcus hemolyticus and Bacillus friedländer in enclosed chambers, infection taking place by inhalation. All mice were autopsied, cultures taken from lungs and heart's blood and the number noted showing pneumonia with or without consolidation. A very small percentage of normal mice exposed to pneumococci died but this percentage greatly increased in animals alcoholized. A total of 1001 mice were exposed to the pneumococcus—216 to Streptococcus hemolyticus and 169 to Bacillus friedländer. In the case of the pneumococcus the organisms rapidly disappeared from the lungs and only an occasional mouse succumbed to pneumococcus septicemia. Upon alcoholization a large percentage died within five days of exposure. In using Streptococcus hemolyticus and Bacillus friedländer the organisms could be recovered

from the lung and blood for a number of days after exposure, and a large number died of septicemia during thirty days after spraying. The longer the organisms persisted in the lungs, the more certain the fatal issue. In another paper the same authors (*Jour. Exper. Med.*, 1925, **41**, 631) give details of the pathology of the experimental pneumonias above described. Sections fixed in Zenker's were stained with eosin and methylene blue and modified Gram's stain. Twenty-eight pneumonia lesions in 80 mice were studied, all of which showed the organism concerned present in lungs and blood. The initial lesion in all seemed to be a polymorphonuclear infiltration of the interstitial tissue. In pneumonias occurring spontaneously in stock mice the lesion is usually a mononuclear response. In the early stages the three types can only be differentiated bacteriologically. Later they assume individual pathological characters. The result of the study would indicate that the term "broncho" may not be aptly applied to the lesions, but that "interstitial," "lobular" and "lobar" would be more expressive. The experimental pneumonias seemed, according to the authors, to be of the nature of a cellulitis of the lung, with the initial lesions in the lower respiratory tract, around the bronchioles, atria and alveoli. An indifferent plate illustrates the second paper.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

Eight Weeks' Quinin Treatment for Malaria.—GRIFFITHS (*Pub. Health Rept.*, 1925, **40**, 538) tried quinin for the purpose of malaria control from the public health point of view, with results which were not very satisfactory, as shown by the following conclusions: (1) Under arrangements as satisfactory as could be made for having the eight weeks' quinin treatment for malaria taken by rural people as represented by the group herein considered, it was not practicable to get the entire treatment taken as recommended. (2) Sufficient effect from quinin was secured to prevent frank manifestation of malaria in 90.6 per cent of the persons treated, but in 25.4 per cent of the group parasites were found on examination of thick smears after the supervisory treatment, and before sufficient time had elapsed for new infections to show in the blood; in the group of 74 people treated, 36.5 per cent were positive on blood examination before treatment; after the

treatment 25.4 per cent showed parasites, a reduction of only 11.1 per cent. (3) In a heavily infected, poorly-nourished population, with a probable high rate of hookworm disease the quinin treatment, as taken, failed to free a large percentage of cases of either asexual or sexual forms of the parasites, but did prevent to a great degree the development of paroxysms. (4) From the last week of August to the second week of November, during which time no supervisory quinin treatment was given, the increase of infections, as shown by examination of thick blood smears, was 46.6 per cent, the great increase being due largely to the number of infections by P. falciparum. (5) If the late season infections were newly acquired infections the transmission occurred through a relatively small number of vectors with an increasingly high number of gametocyte carriers toward the end of the season.

Vaccination by Mouth Against Bacillary Dysentery.—ENLOWS (*Pub. Health Rept.*, 1925, **40**, 639) reviews previous work on the subject and presents experiments of her own, and the following summary and conclusions: (1) It is pointed out that the method of vaccination by mouth is not new; it was used more than nineteen years ago in an effort to produce immunity to the Shiga type of bacillary dysentery; renewed interest in the problem followed Besredka's experiments, in which he introduced the use of beef bile as an erosive agent, preparing the way for the entrance of the subsequently ingested bacilli into the deeper lying cells of the mucosa which he considered responsible for the local immunity. (2) A brief review of some of the early work is given, and also of the work done since Besredka's experiments, including a few of the experiments (foreign) on man; these experiments are somewhat contradictory in that at least a part of the animal experiments do not seem to confirm the work of Besredka, while all of the human experiments favor this method of vaccination; the human experiments are, however, too few in number to warrant definite conclusions. (3) The author's experiments with rabbits show that the greatest protection (70 per cent) was afforded by the subcutaneous method, but that a fair degree of protection (57 per cent) resulted from the vaccination by mouth, and that there was much less danger involved in the use of the latter method; beef bile is shown not to be necessary in vaccinating by mouth against the Shiga type of bacillary dysentery. While the method of vaccinating by mouth against the Shiga type of bacillary dysentery should still be considered in the experimental stage, two facts are evident: (1) The danger and discomfort are too great to recommend the use of the subcutaneous method of vaccination against the Shiga type of infection. (2) Since vaccines can be so prepared that no danger nor discomfort follows their ingestion, and since at least some immunity is shown to follow such procedure, vaccination by mouth is apparently worthy of further trial.

The Incidence of Illness in a General Population Group.—SYDENSTRICKER (*U. S. Pub. Health Rep.*, 1925, **40**, 279) states that a true picture of ill health, and, therefore, of the problems to be attacked by those who are engaged in preventing disease, is not adequately portrayed by death statistics. The obvious reason for this is that mortality records by definition do not include the cases of illness that are not

fatal, to say nothing of the suffering and the lowered vigor and the lessened efficiency among the living. A study of illness in a general population group in a typical small city not only shows the inadequacy of mortality statistics for this purpose but suggests the kind of picture that complete morbidity records would afford. Looking at it in broad outline only, it was found in the group of persons studied that: (1) Over 100 cases of illness occur annually for each death. (2) More than half of the morbidity was due to respiratory diseases. The ratio of respiratory illnesses to deaths from respiratory causes was more than 300 to 1. (3) Diseases and disorders of the digestive system caused an annual illness rate of 117 per 1,000 but a mortality rate of less than 1 per 1000, a ratio of about 200 to 1. (4) The "general diseases"—epidemic and non-epidemic—composed principally of those diseases against which public health effort has been mainly directed, caused only 11 per cent of all illnesses. (5) While deaths occur principally in infancy and in old age, ill health, as measured by the incidence of illness, occurs with comparatively little variation throughout life. It is prevalent among the young, those in the "prime of life," and the aged without much discrimination. This picture inevitably suggests a point of attack upon the causes of ill health not adequately recognized now—the diseases which are incident between the extremes of life. If, as it is now the custom, success of public-health work is to be measured in money terms, surely no more cogent argument could be put forward than that of the economy of preventing loss of the efficiency of the population at those ages when health means the most in production. It is not hard to figure that a day of sickness prevented at the age of thirty or forty years is more profitable than at the age of seventy years. But, in a broader sense, the diseases which cause ill health are a challenge to the sanitarian, not merely because they have an exhausting effect upon man's power to resist death but because they lessen his ability to achieve and his capacity to enjoy life in the years of his most abundant strength.

The Rickettsiæ and their Relationship to Disease.—WOLBACH (*Jour. Am. Med. Assn.*, 1924, **84**, 723) states that the term "rickettsia" should be applied only to microörganisms adapted to arthropods ("insects") and pathogenic for vertebrates and having the following characteristics: Small size, pleomorphism, slight affinity for anilin dyes and intracellular habitat in the arthropod host. It should be kept in mind that practically nothing is known about the nonpathogenic, rickettsia-like, intracellular microörganisms of arachnids and insects, whether casually present or in the role of symbionts. The work so far done in this field has been superficial and evasive of the main problems concerning relationships between microörganisms and hosts; it has, however, served to obscure the status of the pathogenic rickettsiæ. The Dermacentroxenus rickettsi is the cause of Rocky Mountain spotted fever, and that Rickettsia prowazeki is the cause of typhus the author regards as proved. There is strong presumptive evidence that Rickettsia pediculi is the cause of trench fever. It is certain that the rickettsiæ represent a new group of microörganisms, and probable that other pathogenic ones will be found.

Developments in the Fields of Mental Testing. — DOLAN (*Pub. Health Rep.*, 1924, **39**, 2519–2520) gives the following recapitulation of the data presented in the paper: In summing up the work that has been accomplished in the field of mental testing, mention will be made of only the most salient facts. After the successful application of the Binet-Simon test of general intelligence, interest in this branch of psychology increased. The greatest impetus to the movement came with the advent of war, during which the Army Alpha and Beta tests were organized and successfully applied. Up to the close of the war, work had been done in testing general intelligence only, but the development of the Army tests had opened so many new possibilities that psychologists enthusiastically took up the task of broadening the field and extending its limits. Trade tests and tests rating specific abilities were organized, the number and kinds of general intelligence tests were increased, and, finally, attempts were made to measure temperamental qualities. This process of development laid stress upon the quantity of tests, however, at the expense of their quality. As a result, the real problems of securing accurate measurements were not realized until analyses were made of the quality and reliability of tests already in existence. Then the complexity of mental testing became apparent and the significance of such factors as emotional reactions, correlations, methods of administration, establishment of criteria, and correct analysis were brought to light. Tests as they stand today are by no means perfect as far as the consideration of these factors is concerned. More stress is constantly being laid upon mental testing as an individual problem, and it is by individual testing that the best results are secured, the best not only for the individual but for society. Too much emphasis cannot be placed upon the value of tests in vocational guidance. It is during the school period, when the youth of the country is planning its future, that correct guidance along suitable channels is absolutely essential. It means not only satisfaction and pleasure to the individual, but the utilization of his powers in the field where they are most needed and most valuable. It means satisfaction to the individual, to industry, to society, to the eugenist, to the race. Thus the effects of mental testing are far-reaching and significant, and embrance not only the field of psychology but the fields of psychiatry and of medicine as well. The mental testing movement is still little more than in its infancy. Many intelligence tests have been standardized as giving accurate measurements of general ability. Accurate measurements may also be secured from certain tests of specific abilities and aptitudes. Tests of temperamental qualities are still more or less unreliable. Research agencies throughout the country are industriously carrying on the work, placing more emphasis upon the quality of their tests and making them more reliable. The problem is by no means simple. Tests are far more complicated when gone into qualitatively than one is likely to realize, for it means delving deeper into hidden traits and workings of the human mind that are not yet fully understood or even realized. But when mental tests are standardized and give measurements that may be relied upon, then, if applied to those boys and girls who are in school or just embarking in the field of industry, foundation will be laid for the most fruitful and far-reaching results.

The Relation of Vegetative Activity of Bacteria to Pathogenicity.—FELTY and BLOOMFIELD (*Jour. Exper. Med.*, 1924, **40**, 703) report experiments to show that distinct differences exist between relatively young cultures of bacteria and the same strains during the period of decline as regards invasive power and pathogenicity, and state that these differences must be distinguished clearly from specific alterations in virulence such as those produced by animal passage. The exact interpretation of these observations is not, however, perfectly clear. The authors are inclined to believe that simple alterations in vegetative activity might account for the differences described, but to what extent the results have been due to injury to the bacteria by products of culture growth it is impossible to say, and further work will be necessary to settle this point. The experiments seem to bear definitely on the problem of infection in as far as they show that purely temporary modifications of growth activity whether or not brought about by specific injury lead to changes in invasiveness which are quite analogous to the test-tube phenomenon of lag. It has been previously shown that there exists in the upper air passages a mechanism by means of which foreign particles and bacteria can be eliminated within a few hours. It seems highly likely on the basis of the present work that bacteria entering in an inactive growth phase—for example dried in dust or perhaps from a chronic carrier—may be disposed of before activity can be resumed, whereas organisms introduced in the stage of active growth—as from a case of acute disease—may be able to take advantage of a portal of entry. It is further possible that these experiments may have some bearing on the genesis of epidemics, especially as regards the pre-epidemic phase, and these matters will be discussed at another time.

Notice to Contributors.—Manuscripts intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, Philadelphia General Hospital, 34th Street below Pine, Philadelphia, Pa.

Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively.

All manuscripts should be typewritten on one side of the paper only, and should be double spaced with liberal margins. Illustrations accompanying articles should be numbered and have captions bearing corresponding numbers. For identification they should also have the author's name written on the margin. The recommendations of the American Medical Association Style Book should be followed. It is important that references should be at the end of the article and should be complete, that is, author's name, title of article, journal, year, volume and page (beginning and ending).

Two hundred and fifty reprints are furnished gratis; additional reprints may be had in multiples of 250 at the expense of the author. They should be asked for when the galley proofs are returned.

Contributions in a foreign language, if found desirable for this JOURNAL, will be translated at its expense.